Volume **9** Issue **1** March **2001**

Topics in HIV Medicine™

A publication of the International AIDS Society–USA

Highlights of the 8th Conference on Retroviruses and Opportunistic Infections, Part 1

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About This Issue

This issue is the first part of a 2-part series to summarize proceedings of the 2001 Conference on Retroviruses and Opportunistic Infections. Seven clinicians and researchers in HIV disease highlight selected new data from the Conference, held in Chicago, Illinois from February 4 to February 8, 2001.

Mario Stevenson, PhD, summarizes new work in basic science; Judith S. Currier, MD, and Diane V. Havlir, MD, review research presented on metabolic complications associated with HIV infection and antiretroviral therapy and on HIV and hepatitis coinfection; and Mary A. Albrecht, MD, Eoin P. G. Coakley, MD, Roger T. Inouye, MD, and Scott M. Hammer, MD, provide a comprehensive review of new research on antiretroviral therapy, covering investigational drugs, therapeutic approaches in treatment-naive and treatment-experienced patients, drug resistance, and pharmacology. 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 on the Web at www.retroconference.org.

The May issue of *Topics in* HIV *Medicine* will summarize Conference research on vaccine development and HIV-1 disease pathogenesis as well as lectures from the opening session that focused attention on strategies for the HIV pandemic in the developing world. The May issue will also include updated information on antiretroviral drug resistance from a subgroup of the International AIDS Society–USA Panel on Antiretroviral Resistance.

Unrestricted educational grants supported this issue of *Topics in HIV Medicine* and the 2001 *HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management* program. We gratefully acknowledge:

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Topics in HIV *Medicine* is published 4 to 6 times a year. To obtain a complimentary subscription or notify the International AIDS Society–USA of a change in address, please contact the International AIDS Society–USA at the address listed below or use the Subscription Request/Address Change form at the back of this issue.

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Topics in HIV *Medicine* welcomes editorial correspondence. Address letters to:

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1001 B O'Reilly Avenue, PO Box 29916
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Web site: http://www.iasusa.org
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On The Web
Current and previous issues of *Topics in* HIV *Medicine* are available online at www.iasusa.org.

Printed in USA • March 2001

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Formerly – *Improving the Management of HIV Disease*
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Highlights of Basic Science Research

Mario Stevenson, PhD

Basic science research is a steadily expanding component of the Retrovirus Conference. There were some surprises from studies that addressed the relation between the host cell cycle and permissiveness to viral infection. Several studies provided recent insights into factors that influence virion morphogenesis and release. New findings were presented on the accessory proteins Vpr and Nef. Studies of viral pathogenesis were highlighted by recent reports on attempts to characterize the reservoirs of viral replication in patients who are being treated with antiretroviral therapy. Studies that detailed the identification and characterization of a novel CCR5 antagonist were one of the highlights of the sessions on tropism and coreceptors. In addition, a number of presentations provided updates on studies aimed at identifying the role of DC-SIGN in HIV replication.

Virology

The activities of many primate lentiviral proteins are mediated through cellular ligands, and these interactions appear to be species-restricted. For example, the activity of the viral transacting protein Tat requires interaction with the cellular protein cyclin T1. However, Tat does not function efficiently in murine cells, because it does not interact efficiently with the murine equivalent of cyclin T1. A single amino acid change in the murine cyclin T1 promotes an interaction with Tat and can support Tat action in murine cells. Several groups have noted that, despite restoration of Tat function in murine cells and efficient expression of viral proteins, there is yet another block to viral replication.

Bieniasz (Abstract S10) and Mariani (Abstract 284) reviewed studies in which the appropriate receptor molecules were expressed, as well as cyclin T1, in mouse, hamster, and rat cell lines. These cells supported efficient reverse transcription, and Tat functioned at almost wild-type levels. These cells produced very little virus, which, nevertheless, was as infectious as human cell–produced virus. The viral precursor polyprotein Pr55 Gag appeared to be poorly processed and secreted from mouse and rat cells. When the investigators produced heterokaryons between these cells and human cells, the assembly and release of viral particles was restored. These studies support the notion that human cells contain a factor that promotes Gag processing and viral assembly and release and that the murine equivalent does not function as a cofactor. The identification of this cellular cofactor for viral assembly and release is important for the development of small-animal models of HIV infection. Furthermore, this cofactor is an attractive drug target, and may lead to the development of agents that interfere with late steps in the viral replication cycle.

Continuing with the theme of cellular processes that influence retroviral Gag functions, Goettlinger (Abstract S11) reviewed studies that point to a role for cellular ubiquitin ligase in promoting the action of Gag during virus release. Goettlinger discussed research from 3 groups that showed that ubiquitin plays an important role in a late step in viral budding. Ubiquitin targets proteins for proteasomal degradation by binding through a C-terminal glycine to lysine residues in the protein. Ubiquitin was previously shown to be contained within viral particles of HIV-1 as well as of murine leukemia virus (MLV). Interestingly, depletion of the intracellular pool of free ubiquitin appears to inhibit the budding step of a number of unrelated RNA-enveloped viruses. By blocking proteasomal function, recycling of ubiquitin is prevented and results in an excess of the unconjugated form of ubiquitin, leading to measurable reductions in the budding of both Rous sarcoma virus and HIV.

It has been suggested that proteasome inhibition leads to an accumulation of defective Gag polyproteins that would normally be subject to proteasomal degradation and that these defective proteins may interfere with budding. Overexpression of truncated forms of the Gag protein of HIV-1 creates a dominant-negative effect on HIV budding. Mice that express a defective Gag product (FV-1 mice) are also highly resistant to viral infection. The ubiquitination of Gag proteins requires an assembly domain in Gag (which is also referred to as a "late" domain) that is required for final detachment of the virion from the plasma membrane. Goettlinger presented evidence that late domains are contained within the Gag proteins of a variety of viruses, including HIV, MLV, and Ebola virus. Goettlinger presented a model in which ubiquitin ligase is recruited to the site of viral budding through interaction with late domains within Gag. The conservation of a ubiquitin-dependent budding mechanism by diverse viruses strongly supports the importance of such an activity in the replication cycle of these viruses and further illustrates how viruses use cellular processes to complete their life cycle.

On infection of the cell, retroviruses initiate reverse transcription of viral complementary DNA within a high-molecular-weight nucleoprotein complex that is commonly referred to as a reverse transcription complex. The composition and nature of the reverse transcription complex remains poorly understood, and McDonald (Abstract 281) presented what may be the first electron microscopy images of the complex. Studies indicate that HIV reverse transcription complexes contain the enzymatic proteins integrase and reverse transcriptase, the structural protein matrix, and the accessory protein Vpr. By conjugating Vpr with green fluorescent protein, incoming reverse transcription complexes could be visualized by fluorescence microscopy. Furthermore, the investigators prepared virions in the presence of fluorescently labeled deoxynucleotides, with the result being that genomic viral RNA within incoming reverse transcription complexes could be further visualized by fluorescence microscopy. Time-lapse observations of incoming reverse transcription complexes suggested that these

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complexes move through cells along microtubules. Using correlative electron microscopy with labeled reverse transcription complexes, the investigators obtained high-resolution images of cytoplasmic reverse transcription complexes. The images suggested a cylindrical structure with a diameter of 100 to 120 nm. Surprisingly, reverse transcription complexes that were derived from cells infected with wild-type HIV-1 or vesicular stomatitis virus–pseudotyped HIV showed that these cylindrical reverse transcription complexes have a globular structure at one end. Since these complexes appear to be larger than the viral core, these results suggest a considerable reorganization of virion components during the formation of the reverse transcription complex. These studies may provide important information on a rather elusive step in the retroviral replication cycle.

The current models of HIV-1 assembly indicate that the major precursor polyproteins Gag and Gag/Pol, from which the structural and enzymatic proteins are derived, respectively, interact at the plasma membrane before virion maturation and assembly. The results of studies presented by Khorchid (Abstract 280) challenged this popular view and indicated that this interaction may occur in the cytoplasm independently of plasma membrane binding. The interaction of Gag and Gag/Pol precursors with the plasma membrane is mediated through a myristic acid moiety at the N-terminal matrix domain of the precursors. Nevertheless, nonmyristylated precursors were able to interact in the cytoplasm. In addition, the interaction of the NC domain of Gag with genomic viral RNA directs the packaging of viral RNA within virions. Khorchid and colleagues showed that the interaction of Pr55 Gag with genomic viral RNA was necessary for interaction between the 2 major precursor polyproteins. These studies further define events in retroviral replication that are required for proper assembly of virions within the infected cell.

The action of reverse transcriptase requires interaction between the p66 and p51 subunits of reverse transcriptase. Previous studies have suggested that mutations within the nonnucleoside reverse transcriptase inhibitor (NNRTI)–binding site within reverse transcriptase can influence the interaction between reverse transcriptase subunits. A study presented by Tachedjian (Abstract 282) found that NNRTIs, which are allosteric inhibitors of HIV reverse transcriptase, affect heterodimerization of the p66 and p51 reverse transcriptase subunits. By fusing p66 and p51 subunits to lexA and gal4AD, respectively, the investigators could examine interactions between p66 and p51 subunits in a 2-hybrid assay in yeast. The investigators found that inhibitors such as efavirenz, nevirapine, and several other NNRTIs markedly promoted p66 and p51 heterodimerization. Delavirdine, which interacts with reverse transcriptase at a site different from that of most other NNRTIs, did not increase heterodimerization. Variants of p66 that contain NNRTI resistance mutations (Y181C) were insensitive to increases in heterodimerization by nevirapine. This study found a previously unsuspected effect of NNRTIs on the heterodimerization of reverse transcriptase. The authors suggest that the interaction of drug with a p66 subunit may create the conformational change that increases its binding to the p51 subunit. This study provides a clear example of how basic research investigations in the structure and function of viral enzymes can point to new strategies to broaden the efficacy of the currently available antiretrovirals.

Accessory Proteins

HIV-1 Vpr is a virion protein that has been shown to promote nuclear targeting of viral preintegration complexes in nondividing cells such as macrophages. Consistent with this activity is the finding that Vpr, when expressed in the absence of other viral proteins, localizes to the nucleus. This creates a paradox in that Vpr must interact with Gag and be transported to the cellular plasma membrane for incorporation into maturing virions. Yet, during viral entry, Vpr must travel in the opposite direction while promoting nuclear localization of the viral reverse transcription complex.

The results of studies presented by Sherman (Abstract 139) and Vodicka (Abstract 140) further suggested that Vpr has the characteristics of a nucleocytoplasmic shuttling protein. To follow the movement of Vpr within cells, the investigators fused Vpr to fluorescent proteins. The wild-type Vpr protein localized predominantly to the nucleus and nuclear envelope, but a truncated form of Vpr (amino acids 1–71) was localized exclusively to the cytoplasm. Furthermore, mutations within a putative nuclear export signal in Vpr also resulted in cytoplasmic localization of the protein. The antibiotic leptomycin B, an inhibitor of the mammalian nuclear export receptor Crm1, caused nuclear accumulation of Vpr_{1-71}. The findings in these studies are consistent with the notion that Vpr continuously shuttles between the nucleus and the cytoplasm and that nuclear export is mediated by Crm1, a major cellular nuclear export receptor.

The functional significance of this nuclear export activity of Vpr remains unexplained. One possibility is that the nuclear export activity of Vpr maintains a sufficient concentration of cytoplasmic Vpr for packaging into assembling virions. Surprisingly, however, the inhibition of Vpr export by leptomycin B did not decrease the amount of Vpr that was contained within virions. Since the virion incorporation of Vpr depends on interaction with the p6 domain of Gag, one possibility is that a previously reported nuclear export activity in Gag (Dupont et al, *Nature*, 1999) may maintain cytoplasmic localization of Vpr even if its nuclear export activity is impaired. An important question that stems from these studies is why the nuclear export activity of Vpr does not interfere with its reported role in promoting nuclear uptake of viral reverse transcription complexes during viral entry. Following viral infection, reverse transcription complexes that localize to the nucleus would be rapidly exported back to the cytoplasm through the action of Vpr. Presumably, therefore, the nuclear export activity of Vpr must somehow be suppressed in the acutely infected cell. One possibility is that the shuttling activities of Vpr are influenced by posttranslational modifications in the protein such as phosphorylation. A study by Zhou and Ratner (Abstract 137) suggested that Vpr is phosphorylated on serine and that this phosphorylation can influence the ability of Vpr to inhibit host cell cycle progression. Thus, phosphorylation of Vpr may impair or promote nuclear export, thereby influencing the steady-state localization of Vpr within the infected cell.

The aforementioned studies suggest that the nuclear export of Vpr is mediated through the cellular nuclear export receptor Crm1. The HIV-1 Rev protein, which regulates the splicing of viral messenger RNA, was the first viral protein to be shown to have nucleocytoplasmic shuttling activity. Nuclear export of Rev also depends on Crm1. Daelemans and colleagues (Abstract 283) described the identification of a low-molecular-weight compound that inhibits Crm1-mediated nucle-

ar export and further inhibits Rev function in human cells. The drug reversibly inhibits the binding of Rev to Crm1. It should be emphasized that such agents are unlikely to be used as antiviral agents. Since Crm1 mediates the nuclear export of a diverse variety of cellular proteins, its inhibition is likely to be accompanied by considerable cellular toxicity. Nevertheless, this drug may prove to be an important reagent in further defining the interplay between viral proteins and the nuclear export apparatus of the cell.

The accessory protein Nef greatly facilitates viral replication and pathogenicity in vivo. A number of activities have been described for Nef. Among these is the facilitation of viral entry in certain cell types. For example, viral infectivity of HeLa cells that express CD4 is increased by Nef, and this has previously been suggested to reflect an increase in the extent of reverse transcription in the target cell. The results of studies presented by Cavrois (Abstract 279) raised the intriguing possibility that Nef may facilitate the cytosolic entry of the virus. When virions bind specifically to receptor and coreceptor molecules on the cell surface the viral membrane fuses with the cellular plasma membrane. In a poorly understood process referred to as "uncoating," the capsid core disassembles and releases genomic viral RNA together with associated virion proteins into the cytosol. The investigators examined the cytosolic association of Gag p24 as a surrogate marker for viral entry. They observed that, while the presence of an intact *nef* gene significantly enhanced cytosolic entry of virions following CD4- and chemokine receptor–dependent entry, the enhancing effect was impaired by mutations in *nef* that had previously been shown to affect the CD4-downregulating activity of *nef* or by mutations in SH3 motifs in *nef* that mediate the interaction with protein tyrosine kinases. Surprisingly, the cytosolic entry of HIV-1 virions pseudotyped with MLV envelopes was also enhanced by Nef. In contrast, virions pseudotyped with vesicular stomatitis virus G envelope were not affected by Nef, suggesting that Nef enhances fusion-mediated entry but not entry that occurs through endocytosis. These studies raise the intriguing possibility that some of the effects of Nef in promoting viral uptake may be mediated through another virion protein. Whether Nef influences the fusion or uncoating steps of viral entry is not yet known.

Nuclear translocation of viral nucleic acids in acutely infected cells has been shown to be promoted by at least 3 virion proteins, including the structural matrix protein, the viral enzyme integrase, and the accessory protein Vpr. The nuclear import activity of these proteins has been shown to be mediated by an interaction with members of the importin family of cellular nuclear import receptors. The findings in studies presented by De Noronha (Abstract 141) point to a novel mechanism through which Vpr may promote nuclear translocation of viral reverse transcription complexes. The investigators showed that the expression of Vpr within cells can influence the subcellular trafficking of cell cycle–regulating proteins fused to GFP. It was found that Vpr induces a loss of nuclear integrity, which leads to the admixing of nuclear and cytoplasmic components. Vpr mutants that did not cause cell cycle arrest did not influence nuclear architecture. The authors showed that the changes in the nuclear envelope resulted from a disruption in the nuclear lamin structure. The authors hypothesize that nuclear localization of large viral reverse transcription complexes in nondividing cells may be facilitated by the disruption of nuclear envelope integrity by Vpr.

Tropism

The coreceptor used most frequently for entry of HIV-1 into macrophages is CCR5. Brain macrophages and microglia are the predominant, if not the exclusive, infected cells in the brain. However, it is not clear whether macrophages and brain microglia share similar coreceptor requirements for viral entry. Studies by Gorry and colleagues (Abstract 5) compared brain-derived viral isolates for their ability to replicate within monocyte-derived macrophages and microglia and for their coreceptor use. Isolates that replicated to high levels in monocyte-derived macrophages also replicated to high levels in microglia. Surprisingly, viral fusogenicity in macrophages, rather than CCR5 use, correlated with infectability for microglia. Furthermore, highly fusogenic X4 isolates were more able to infect microglia than poorly fusogenic R5 variants. The authors suggest that dual-tropic and highly fusogenic viruses may contribute to the neuropathologic manifestations of AIDS.

Dendritic cells have been implicated in viral dissemination. The current models suggest that dendritic cells trap virions and promote infection of T cells in *trans*. A presentation by van Kooyk (Abstract L10) discussed ongoing studies to characterize lectins that promote virion binding to dendritic cells. The investigator had previously identified DC-SIGN as an HIV receptor. Although DC-SIGN does not function independently as a receptor for viral entry, it is able to support *trans* infection of T cells that express the appropriate receptors. The results of studies presented by Lee (Abstract 529) suggest that DC-SIGN, when expressed in *cis*, can mediate more-efficient use of rate-limiting minor coreceptors. When expressed in *cis* and in conditions in which the coreceptor levels were limiting, DC-SIGN significantly increased the use of the coreceptors, including STRL33/BONZO, CCR2, APJ, and, to a lesser extent, the major coreceptors CCR5 and CXCR4. Coexpression of DC-SIGN conferred on some viruses the ability to use STRL33/BONZO to infect cells—they are unable to do so in the absence of DC-SIGN. The requirement for CD4 and a coreceptor was not alleviated by the expression of DC-SIGN. In addition, DC-SIGN was unable to increase infection through coreceptors when it was expressed in *trans*. The enhancing effects of DC-SIGN were further observed when it was expressed in *cis* on 293 fibroblasts. These studies show the importance of DC-SIGN in mediating the ability of dendritic cells to transmit virus to T cells. One feature of dendritic cell–T cell interaction involves the transinfection of resting cells by HIV. It is not clear whether DC-SIGN plays a role in the subsequent activation of T cells that are infected after contact with dendritic cells.

Laboratory-adapted HIV-1 isolates typically have X4 tropism. Despite the presence of CXCR4 on macrophages, these cells do not support efficient infection of laboratory-adapted isolates. Studies summarized by Tokunaga (Abstract 532) found that the expression of elevated levels of CD4 on macrophages increases the infection of primary X4 isolates but not laboratory-adapted isolates, and suggest that the cell surface levels of CD4 may be limiting for infection of primary macrophages by primary HIV-1 isolates.

Cyclophilin A is a cellular target of the immunosuppressive drug cyclosporine. Cyclophilin A is packaged into virions through interaction with the capsid domain of the Gag polyprotein. Virion-associated cyclophilin A significantly increases viral infectivity; however, the mechanism by which infectivity is increased is not well understood. Findings presented by Yurchenko (Abstract 114) and Bukrinsky (Abstract 530) identified a cyclophilin A–binding protein (CD147)

that uses a yeast 2-hybrid screen. The expression of CD147 in CHO cells increased HIV-1 entry. Viruses that contained mutations in Gag that disrupted interaction with cyclophilin A were not enhanced by CD147. Antibodies to CD147 inhibited viral uncoating, as evidenced by a reduced dissociation of HIV-1 core proteins from the membrane. The authors presented a model in which virion-encapsidated cyclophilin A interacts with CD147 of the target cell and this interaction promotes the uncoating step of viral entry.

Arguably, one of the most exciting developments in drug discovery presented at the conference was the identification of a new CCR5 antagonist. Reyes (Abstract L11) described the leading compound SCH C that inhibited both RANTES and MIP-1 □ binding to CCR5. SCH C had subnanomolar antiviral activity against R5 isolates but had no effect on X4 isolates. Surprisingly, SCH C could suppress viral replication even if it had been removed from the cells 25 hours before viral infection. In vitro propagation of R5 virus in the presence of SCH C resulted in the emergence of viral mutants that were greatly resistant to SCH C. Surprisingly, these resistant variants still maintained R5 tropism rather than having switched to an X4 phenotype, and the resistant variants were still sensitive to inhibitors of R5 entry. In addition, viruses passaged in SCID-HU mice in the presence of SCH C acquired resistance, but without having switched from the R5 to the X4 phenotype. A second-generation compound called SCH D, which is approximately 10-fold more potent than SCH C, was also discussed. These compounds are exciting new potential additions to the armamentarium of agents to combat HIV infection.

Pathogenesis

According to the current models of primate lentiviral replication, productive infection of CD4+ T cells requires that they be in cell cycle. Resting (G_0) T cells are refractory to infection because of rate-limiting levels of coreceptor, because of low levels of deoxyribonucleoside triphosphate, which limit the extent of reverse transcription, and because of inefficient nuclear localization of viral nucleic acids. Studies have suggested that T cells must be in the G_{1B} stage of cell cycle or beyond to support productive infection. Several presentations provided surprising findings that, under certain conditions, HIV-1 can apparently infect and replicate within noncycling T cells.

Goldsmith (Abstract S18) presented findings on the characteristics of HIV replication in human lymphoid histocultures. This culture system, which was originally described by Margolis, consists of tonsil and spleen explants that are maintained as "raft" cultures and are highly permissive to HIV infection. Goldsmith compared the replication characteristics of X4 and R5 viruses within the histocultures and showed that, although R5 viruses infect fewer T cells than X4 viruses, the extent of viral replication, as indicated by the amount of secreted p24, is the same with both viruses. Goldsmith also found that viruses that lack Vpr, an accessory protein that has been shown to facilitate the infection of macrophages in vitro, infected far fewer macrophages in these histocultures. Surprisingly, a substantial proportion of the infected T cells in these lymphoid histocultures appeared to be in the G_0/G_{1A} phase of the cell cycle and had a naive cell phenotype. Both X4 and R5 viruses were able to infect naive resting T cells. Furthermore, the presence of p24 antigen in these naive resting T cells suggested that they were permissive for productive viral infection. The investigators ruled out that T cells were infected while in cycle. They further showed that naive cells produce HIV at lower levels than do memory cells. This infection was cytopathic, since these naive resting cells were depleted from these histocultures.

Continuing with this theme, Scales and colleagues (Abstract 80) found that in dendritic cell–T cell cocultures HIV replication was observed in T cells that lack activation markers. Collectively, these studies support the notion that primate lentiviruses can productively infect noncycling T cells. At present, it is not clear whether the productively infected cells are truly quiescent "G_0" lymphocytes or whether these cells are in a very early stage of cell cycle. Since T cells in vitro are not susceptible to HIV infection unless they have been stimulated to enter cell cycle, the microenvironment of the histoculture or the dendritic cell–T cell environment may provide signals such as cytokines that promote the permissiveness of noncycling T cells. Previous studies by the Littman laboratory have found that certain cytokine combinations are sufficient to render noncycling T cells permissive to HIV infection. These studies further extend observations by the Haase group, who found infection of noncycling T cells during SIV and HIV infection. It will be important to determine the extent to which noncycling T cells support HIV replication in vivo, since these cells may have very different turnover characteristics than infected cells that are in cell cycle, and the presence of a reservoir of infected noncycling cells may have considerable implications for viral latency and persistence.

Another presentation indicated that natural killer cells may be susceptible to HIV infection in vivo. Valentin and colleagues (Abstract 505) used 4-color flow cytometry combined with real-time polymerase chain reaction to characterize populations of infected cells in patients who are being treated with highly active antiretroviral therapy (HAART). Using this approach, the investigators identified a subpopulation of natural killer cells that expressed CD4 as well as the coreceptors CCR5 and CXCR4. Proviral DNA was detected in purified natural killer cells from a large percentage of the HIV-1–infected patients, and this proviral DNA appeared to be very stable for up to 18 to 24 months in these patients. Further study is clearly warranted to determine the role of natural killer cells in maintaining viral persistence in the face of HAART.

Complications of HIV Infection and Its Therapies

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

The term lipodystrophy has often been broadly applied to describe both body shape changes and other metabolic abnormalities that occur during the course of HIV infection. To date, a standard definition for this term has been elusive but several groups are actively working toward this goal. Many (but not all) of the studies presented at the Conference reflect the growing trend to investigate the components of this syndrome as distinct but possibly related clinical phenomena. Increasingly, objective measures are replacing self-reports and a few randomized studies are beginning to appear. Following this trend, this section of the Conference review is divided into specific metabolic complications (body shape changes, lipid abnormalities, bone disease, lactic acidosis, and cardiovascular disease). New research on antiretroviral switch strategies and hepatitis coinfection are also reviewed.

Body Shape Changes

Data from several cohort studies have identified an association between the duration of HIV infection and the development of body shape changes. At last year's meeting we learned that lipid changes were common in a small group of patients treated during primary infection. Further evidence that patients treated during primary HIV infection are at risk for developing body shape changes was described by Goujard and colleagues (Abstract 403) in their prospective study of 121 patients diagnosed and treated with antiretroviral therapy during primary HIV infection. The presence of "lipodystrophy" was assessed by physical examination. The cumulative incidence of lipodystrophy increased over time, and was reported to be 6% at 12, 18% at 24, and 30% at 36 months. Of note, patients with lipodystrophy tended to have higher CD4+ and CD8+ T cell counts and lower HIV RNA levels at the last visit. These findings suggest a possible role for immune reconstitution in the pathogenesis of these changes.

The prevalence of body shape changes has varied widely in earlier studies, and has rarely been considered in the context of age- and race-matched HIV-uninfected controls. An important report at this year's meeting, by Kingsley and colleagues (Abstract 538), compared the prevalence of body shape changes and lipid abnormalities among HIV-seropositive men grouped by treatment history and among HIV-uninfected men in the Multicenter AIDS Cohort Study (MACS). Body shape changes were characterized as either peripheral fat wasting or central fat accumulation and were stratified into mild, moderate, and severe. The preliminary report focused on physical examination findings and laboratory parameters only and not on patient self-reports. A third of the HIV-seronegative men and 2 thirds of the HIV-seropositive men were noted to have body shape changes.

The finding that best distinguished the groups by their HIV status and treatment history was the combination of moderate or severe peripheral fat wasting and central fat accumulation. The presence of both of these changes was noted among 20% of the men who were treated with highly active antiretroviral therapy (HAART) but in few of those who were not being treated with antiretroviral drugs or who were being treated with monotherapy or combination therapy and in few of the HIV-seronegative controls. The finding of central fat accumulation alone was not more common among HIV-seropositive men than the age-matched control group. In addition, the prevalence of body shape changes appeared to increase with time on HAART (20% at 2 years) but no further increase was noted out to 4 years of follow-up. Metabolic abnormalities that were more common among the men treated with HAART than among the controls were low levels of high-density lipoprotein (HDL) and high triglyceride, glucose, and fasting insulin levels. The prevalence of lipodystrophy among the HAART-treated MACS participants was similar to that reported from a series of patients treated with HAART for the first time (18%) (Rubio et al, Abstract 646). These results highlight the need to include HIV-uninfected control groups in studies of the metabolic complications of HIV infection. The apparent plateau in the prevalence of lipodystrophy over time warrants further investigation.

Several cohort studies have identified an association between exposure to stavudine and an increased risk of developing peripheral fat atrophy. Unfortunately, most of these reports have been limited by their cross-sectional design and the strong correlation between use of stavudine and longer durations of HIV infection. Joly and colleagues (Abstract 539) presented results of the NOVAVIR study, in which patients with prior use of zidovudine, didanosine, or zalcitabine were randomized to receive either stavudine or zidovudine combined with lamivudine and indinavir. Body shape changes were assessed by a physician at one time point approximately 30 months into the study. Importantly, the groups were well matched at study entry in terms of prior nucleoside reverse transcriptase inhibitor (nRTI) use and duration of therapy and by CD4+ cell count and viral load. Subjects assigned to stavudine were more likely to develop fat atrophy than those in the zidovudine arm, and the differences were statistically significant. The proportion of patients with fat atrophy in 2 or more body areas was 44% in the stavudine arm compared to 18% in the zidovudine arm, (P = .003). In addition, female sex was identified as a predictor of a higher risk for fat atrophy. No difference was noted in the prevalence of fat accumulation between groups. Despite the potential bias of an open-label design, these results are strong evidence that stavudine may play a unique role in the development of lipoatrophy. Results from ongoing blinded studies in treatment-naive patients will be important to corroborate these findings.

How do age and race and ethnicity

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influence the risk of developing body shape changes? In adults, older age has been associated with an increased risk of developing body shape changes; unfortunately, this does not mean that children are spared this complication. Several reports of small series of HIV-infected children (Abstracts 649, 650, 651, 652, and 653) described changes both in lipid and insulin levels and in body composition. In one of these reports (Meneilly et al, Abstract 650) the prevalence of body shape changes among children was 18% and an association with stavudine use was identified.

Previous research has identified a higher rate of body shape changes in whites than in blacks or Hispanics. Chang and colleagues (Abstract 648) examined the prevalence of body shape changes and lipid abnormalities in a cross-sectional study of 122 Koreans. As predicted, the insulin and triglyceride levels were higher and the HDL cholesterol levels lower in the HAART-treated patients. However, no difference was noted in the ratio of trunk to appendicular fat (as measured by dual-energy x-ray absorptiometry) between the HAART-treated patients, the treatment-naive patients, and the controls. It was not clear whether the absence of fat redistribution was related to a short duration of HAART therapy; regardless, these results are further evidence that genetics may play a role in the development of abnormal fat distribution.

One of the issues that continue to hinder the study of body shape changes is the need for reliable and low-cost measures of body composition. Andrade and colleagues (Abstract 644) compared an anthropometric measure of body fat (using the Durnin-Wormersley equation) with magnetic resonance imaging (MRI). The main finding of this study was that the calculations of total adipose tissue and subcutaneous adipose tissue with the low-cost Durnin-Wormersley equation correlated best with the MRI findings and that the estimation of visceral adipose tissue using this formula was less accurate. These results have implications for use in prospective studies that are focused on changes in subcutaneous fat. Viciana and colleagues (Abstract 645) compared the measurement by calipers of skin-fold thickness in the cheek adipose area of the face (Bichat's area) with self-reports of facial fat wasting and found a very strong correlation. The correlation between caliper measures and MRI findings and the reliability of the caliper measure to capture changes over time remain to be demonstrated, but these preliminary results hold promise for use in prospective studies.

An entire section of an afternoon poster session this year was dedicated to mechanisms and pathogenesis of the lipodystrophy syndrome. While none of these studies presented in this session were conclusive, they provide evidence that many groups are diligently pursuing several avenues of research toward understanding the pathogenesis of metabolic complications in HIV infection.

A direct etiologic link between mitochondrial injury and body shape changes is yet to be established. One challenge to unraveling this potential pathogenic mechanism is the identification of a reliable measure of mitochondrial function in vivo. Several groups working in this area presented preliminary results at this year's Conference. Shikuma and colleagues (Abstract 665) reported on the use of a semiquantitative analysis of tissue-specific mitochondrial DNA (mtDNA) content from samples of subcutaneous fat in a cross-sectional study. They reported decreased amounts of mtDNA levels among subcutaneous adipose tissue of lipodystrophic individuals treated with nRTI-containing HAART therapy compared to nonlipodystrophic patients or HIV-seronegative controls. Of note, specific mutations in the mtDNA were not found. Vigano and colleagues (Abstract 651) used flow cytometry to examine mitochondrial function by measuring markers of mitochondrial membrane potential and apoptosis in peripheral blood lymphocytes. Signs of mitochondrial toxicity were not present in HAART-treated children with or without lipodystrophy. These preliminary results suggest that peripheral blood lymphocytes, while readily available, may not be the best cells in which to evaluate mitochondrial function in vivo. Further work is clearly needed to make the link between mitochondrial dysfunction and body shape changes in HIV infection.

Alterations in lipid metabolism either as a direct result of protease inhibitor therapy or caused indirectly by HIV infection are also under study. Sekhar and colleagues (Abstract 663) characterized lipid kinetics by conducting stable-isotope studies of triglyceride clearance in 6 HIV-infected subjects with fat redistribution and compared the results with those in age- and sex-matched HIV-uninfected controls. Increased rates of whole body lipolysis as well as decreased rates of triglyceride clearance were identified in the HIV-infected subjects compared to controls. The stimulus for these alterations in lipid metabolism as well as the time course between these changes and the onset of body shape changes remains undefined. Other reports described the greater down-regulation of low-density lipoprotein (LDL) receptors in HIV-infected patients compared to controls (Petit et al, Abstract 661) and in vitro upregulation of scavenger receptor class B, type I (a molecule responsible for the transfer of cholesterol from HDL to cells) by saquinavir and amprenavir in vitro (Smart et al, Abstract 662).

Lipid Abnormalities

Elevations in triglyceride and reductions in HDL cholesterol levels appear to be the predominant lipid abnormalities reported in HIV infection. There is strong evidence that some of the protease inhibitors (specifically ritonavir) directly increase triglyceride levels and that decreased HDL cholesterol levels are a feature of chronic HIV infection. Several studies described the lipoprotein profiles in prospectively collected samples from patients enrolled in antiretroviral studies. Data from the Atlantic study (Van der Valk et al, Abstract 654B) found that nevirapine-treated patients had striking improvements in HDL cholesterol from baseline (37.9 mg/dL) to week 24 (50.4 mg/dL). No improvements were noted in the indinavir- or triple-nRTI–treated patients.

Current interventions to treat lipid disorders include diet, exercise, and the use of lipid-lowering agents. Few prospective randomized trials that evaluate any of these interventions have been reported. Miller and colleagues (Abstract 540) reported the preliminary results of a randomized double-blind study in 38 patients of gemfibrozil for the treatment of protease inhibitor–associated hypertriglyceridemia. After 12 weeks there was a modest reduction in the triglyceride levels in the gemfibrozil-treated group, with no changes in the total cholesterol or HDL cholesterol levels. The small sample size makes it unlikely that the trial would identify a statistically significant effect. Importantly, the treatment was well tolerated. Gemfibrozil therapy may not be sufficient to normalize triglyceride levels in the setting of continued protease inhibitor use; however, the reduction provided may be of some clinical benefit over time.

Bone Disease

At the 7th Retrovirus Conference last year, 2 independent groups reported that antiretroviral therapy was associated with osteopenia and osteoporosis. Many additional reports at this year's Conference expanded on the epidemiology of this complication. Osteoporosis, osteopenia, and avascular necrosis are well documented in the absence of antiretroviral therapy in HIV infection, and their incidence appears to increase with the progression of HIV disease. Whether or how antiretroviral therapy accelerates this process remains controversial.

Negredo and colleagues (Abstract 626) reported that antiretroviral therapy was associated with increased risks for osteopenia and osteoporosis. Other reports emphasized that untreated HIV infection is also associated with bone disease (Abstracts 627, 628, 629, and LB8). These relatively small cross-sectional studies could not demonstrate a relationship between antiretroviral therapy and bone disease. Lawal and colleagues (Abstract 627) reported that the rates of osteopenia in antiretroviral-treated and untreated patients with HIV infection did not differ, but were significantly higher than those in matched HIV-uninfected individuals. Similar findings were reported in a cross-sectional study by Knobel and colleagues (Abstract 629) of 80 HIV-infected subjects. Baseline assessments of 151 treatment-naive patients participating in a tenofovir trial by McGowan and colleagues (Abstract 628) found that the criteria for osteopenia were met in 23% of the subjects.

In a cross-sectional case control study of bone mineral density (BMD) reported in the Late Breakers session (Arpadi et al, Abstract LB8), rates of bone disease were significantly higher in the perinatally infected children (aged 4 to 15 years) than in age-matched HIV-uninfected controls. The duration of HIV infection, but not of antiretroviral therapy, was the most important predictor of BMD changes. In a cross-sectional study of 40 children, Vigano and colleagues (Abstract LB9) used a combination of serum markers for bone turnover and imaging techniques to show that bone demineralization was higher in children treated with antiretroviral therapy than in those not treated. In view of other data presented at the Conference, interpretation of these findings was limited by the small size (5 subjects) in the antiretroviral-naive group.

Avascular necrosis is a less frequent, but nonetheless serious, complication of HIV disease. Increasing rates of avascular necrosis were observed in the Johns Hopkins HIV Clinic Cohort and were greater than those reported in HIV-uninfected individuals (Keruly et al, Abstract 637). Low CD4+ cell count, greater duration of HIV infection, and use of steroids (but not antiretroviral therapy) were associated with increased rates of disease. History of protease inhibitor use was present in 3 cases of Legg-Calvé-Perthes disease reported in the Pediatric AIDS Clinical Trials Group Protocol 219 observational cohort of more than 1000 children (Gaughan et al, Abstract 638). The absence of protease inhibitor use at the time of diagnosis in 2 of the 3 cases suggests that factors other than protease inhibitors are responsible for this disease.

Within cohorts of patients receiving antiretroviral therapy, several investigators have attempted to determine the risk factors for osteopenic disease, including elevations in lactic acid levels or the presence of lipodystrophy. The results of these studies have been conflicting. Carr and colleagues (Abstract 631) reported lower BMD among individuals with lower lean body mass, greater exposure to stavudine, and greater age. Reductions in spinal BMD were associated with hyperlactemia, age, and nRTI treatment duration. Huang and colleagues (Abstract 632) reported reductions in BMD among subjects with increased visceral fat due to antiretroviral therapy use. In contrast, a study by Tebas and colleagues (Abstract 633) did not find an association between intraabdominal fat accumulation and reductions in lumbar spine BMD. In a study by Claxton and colleagues (Abstract 634) monitoring subjects with osteopenia who were switched from a protease inhibitor to a nonnucleoside reverse transcriptase inhibitor (NNRTI) regimen, lactate levels at baseline were not associated with reduced BMD and switching therapy was not associated with changes in bone disease. Growth hormone had no apparent effect on BMD in one small study of 12 subjects (Lawal et al, Abstract 635).

Lactic Acidosis

The syndrome of lactic acidosis has gained increasing attention over the past several years as a complication of nRTI use, but our understanding of this complication is still very incomplete. In a state-of-the art summary of the "Metabolic Complications of HIV-1 Disease" session (Session 64), Dr Andrew Carr proposed a classification scheme for the spectrum of hyperlactemia that has been recognized to date. Individuals with lactate levels greater than 10 mmol/L have "severe" disease, are acidotic, and have highly symptomatic disease. Patients with lactate levels between 5 and 10 mmol/L have "moderate" disease, are rarely acidotic, and are only sometimes symptomatic. Those with lactate levels between 2 and 5 mmol/L have "mild" disease and are neither acidotic nor symptomatic. He estimated that only 2% to 3% of patients with any elevation in lactate levels have symptomatic acidemia. Studies to date point to stavudine use as a risk factor for hyperlactemia, although other nRTIs have also been associated with both mild and severe forms of the disease. In the Perth cohort, Dr Carr reported that elevated lactate levels have been associated with faster progression to lipodystrophy, peripheral neuropathy, and osteopenia. This observation needs to be confirmed in other cohort studies, and causality cannot be assumed.

Asymptomatic elevations in lactate levels were the focus of a study by Vrouenraets and colleagues (Abstract 625). Similar to the findings in previous reports, mild hyperlactemia was observed in 21% of nRTI-treated individuals. The authors emphasized that fluctuations over time in patients with mild elevations are common. Observational longitudinal studies are needed to determine whether such elevations predict drug toxicity before clinicians incorporate this test in routine monitoring of patients.

Lonergan and colleagues (Abstract 624) presented data addressing a very practical management question in patients who develop the symptomatic moderate or severe form of disease: Can nRTIs be safely reintroduced in these patients? In 16 of the 17 subjects in their study stavudine was replaced with abacavir (10 subjects), zidovudine (2 subjects), or both (4 subjects) after a period of therapy interruption. Resumption of therapy has not resulted in syndrome recurrence for a period of 6 months.

Cardiovascular Disease

The concurrence of fat redistribution, lipid abnormalities, and insulin resistance has focused attention on the risk of cardiovascular disease in the setting of HIV infection. Updated reports of ongoing cohort studies tracking the rates of myocardial

infarction (MI) provide little comfort in this regard. Klein and colleagues (Abstract 655) are recording and analyzing the rates of hospital events for coronary heart disease in an open-label-treated cohort of 4541 HIV-seropositive patients and in a group of 41,000 age- and sex-matched controls. With follow-up of now just over 4 years there appears to be no difference in the rates of MI between protease inhibitor–exposed and –unexposed HIV-seropositive subjects. Of greater concern is the finding that the HIV-seropositive group appears to have twice the rate of coronary heart disease compared to the uninfected controls. Whether this could be attributed to unmeasured risk factors (eg, smoking, family history, hypertension) that are more prevalent in the HIV-infected group merits further study. In a similar type of study, researchers (Mary-Krause et al, Abstract 657) analyzed data from the French Hospital Database on HIV on the rates of MI among men observed prospectively since 1989. The incidence of MI per 10,000 person-years appeared to increase with a longer duration of protease inhibitor exposure. The relative hazard of developing an MI in those with more than 30 months of protease inhibitor exposure was 4.7 (95% confidence interval, 0.5–45.4). Once again, the contribution of other risk factors, such as smoking and hypertension, is not accounted for in this type of study. (See also Depairon et al, AIDS, 2001.)

Hypertension is an important risk factor in cardiovascular disease. Several small studies have suggested a link between antiretroviral therapy and the development of hypertension, but this association has not been fully evaluated. In a retrospective study, Hewitt and colleagues (Abstract 651) compared the incidence of hypertension in patients treated with either nelfinavir or indinavir with the incidence in protease inhibitor–naive subjects. The incidence was comparable in the nelfinavir and protease inhibitor–naive groups, and was higher in the indinavir group. Whether this association between indinavir use and hypertension will be confirmed in other studies remains to be seen. Previous reports demonstrating an impact of indinavir on insulin resistance may contribute to our understanding of this preliminary finding.

Managing Complications: Switch Strategies

Substitution of one of the components of a successful antiretroviral regimen as a strategy for managing metabolic complications (so-called switch studies) continues to be used and evaluated. In most cases the drug being replaced is a protease inhibitor and the new agent is either an NNRTI or abacavir. The quality of the switch studies presented continues to improve, with randomized trials predominating at this year's Conference. Included in the session on switch studies were 2 studies that are prospectively evaluating the metabolic effects of protease inhibitor and non–protease inhibitor regimens. One unique study, the SWATCH study (Negredo et al, Abstract 669), is comparing the effects of therapy alternated at 3-month intervals with those of continuous treatment with either stavudine, didanosine, and efavirenz or zidovudine, lamivudine, and nelfinavir. Interim results at 9 months of follow-up suggest a superior virologic and immunologic response in the alternating-therapy group and no differences in the rates of adverse events, but it is too early to draw firm conclusions. A second study (Matheron et al, Abstract 670) compared the metabolic changes among patients randomized to receive fixed-dose lamivudine/zidovudine plus either nelfinavir or abacavir. At 48 weeks of follow-up triglyceride levels were higher in the nelfinavir group, and 6% of the abacavir vs 12% of the nelfinavir group were reported to have clinical manifestations compatible with lipodystrophy.

Results of the other switch studies presented at the Conference are summarized in Table 1. A consistent finding is the improvements in lipid profiles when the NNRTIs are substituted for a protease inhibitor. In addition, lipoatrophy does not appear to regress and insulin resistance persists, especially in the setting of established lipoatrophy, suggesting a possible role for nRTIs (or insulin resistance) in the pathogenesis of fat atrophy.

Hepatitis C Coinfection

Dr Kenneth Sherman provided an overview of the issues surrounding hepatitis C virus (HCV) infection and HIV disease in a state-of-the-art lecture (Session 9). He reminded the audience that HCV infection was present in more than 200 million individuals worldwide and in 4 million in the United States. It is the leading indication for liver transplantation in the United States. In a recent survey of AIDS Clinical Trials Group participants, the prevalence of HCV infections was 16%, with the highest rates in injection drug users. The current generation of diagnostic tests are very sensitive and specific for HCV infection. However, in highly suspect cases with negative antibody test results, HCV RNA testing is indicated. A study by Berggren and colleagues (Abstract 562) shed further light on determinants of false-negative HCV antibody test results. A CD4+ cell count of less than 100/µL was associated with a 50-fold increased risk of a false-negative result. Interestingly, these patients did exhibit antibodies to other viral pathogens, including hepatitis A and B viruses.

The effect of HIV disease on the natural history of HCV disease was explored in several studies. Daar and colleagues (Abstract 35) evaluated HCV clearance in a cohort of patients with hemophilia identified in 1989. There was clearance of HCV in 14% of HIV-uninfected subjects compared with only 3% of HIV-infected subjects. Coinfection with HIV was associated with a 5-fold reduction in spontaneous HCV clearance. Investigators from Parkland Memorial Hospital, in Dallas, came to the opposite conclusion in their study (Jain et al, Abstract 568), in which the HCV clearance rate in patients coinfected with HCV and HIV was 15%. Prognostic factors for HCV clearance were not identified, but the authors did emphasize the importance of HCV RNA testing in HCV antibody–positive patients. The discrepancy between these 2 studies may be due to the differences in patient populations. The patients with hemophilia were probably infected with both pathogens early in life, with numerous and continuous exposures to HCV, and the patients in the Dallas cohort were probably infected later in life, through injection drug use.

Subjects coinfected with HIV-HCV appear to exhibit more rapid progression of hepatitis to fibrosis and liver failure compared to patients with HCV only. Other risk factors for progression to cirrhosis include heavy alcohol consumption and low CD4+ cell count. Several groups evaluated whether cellular and cytokine responses to HCV antigens could explain the higher rates of disease progression. The quantitative changes in immune responses to HCV antigens did not differ between HIV-infected and -uninfected patients in a study by Graham and colleagues (Abstract 563). Intrahepatic compartmentalization of □T cells was demonstrated in a report by Agrati and colleagues (Abstract 565) and was postulated to contribute to hepatic inflammation and fibrosis.

The effect of HCV infection on HIV dis-

Table **1.** Switch Studies Presented at the 8th Retrovirus Conference

Investigators (Abstract No.)	Comparison	No. of Patients	Results/Comments
Martinez et al (668)	Efavirenz vs continuous protease inhibitor	93	• Virologic suppression same in both arms • Insulin resistance improved with efavirenz • Less fat accumulation with efavirenz • Progressive fat atrophy in both arms
Estrada et al (671)	Efavirenz for protease inhibitor Lipoatrophic-lipodystrophy	41	• No improvement in insulin resistance • No improvement in lipoatrophy
Walli et al (672)	Protease inhibitor to abacavir (nonrandomized)	31	• Insulin sensitivity increased with abacavir • Triglyceride and cholesterol levels lower with abacavir
Casado et al (673)	Protease inhibitor to efavirenz or nevirapine	100	• Moderate rates of toxicity • Decreased triglyceride and cholesterol levels • Loss of virologic suppression if prior nRTI use

ease progression has been more controversial and more difficult to define. In contrast to the recently published findings from the Swiss cohort study in *Lancet*, Sulkowski and colleagues (Abstract 34) reported no influence of HCV infection on HIV disease progression (defined as progression to an AIDS-defining illness and a decrease in the CD4+ cell count to less than 200/µL). The increase in the CD4+ cell counts associated with HAART was, however, significantly lower in patients with HIV and HCV coinfection than in those with HIV infection only. This difference was also observed in a cohort of patients with HIV and HCV coinfection who were treated with HAART in a study by Torriani and colleagues (Abstract 575). Two additional studies (Rancinan et al, Abstract 570; Macias et al, Abstract 571) evaluating the influence of HCV infection on mortality in HIV-infected patients in the HAART era failed to implicate hepatitis C as an independent risk factor for death. In a cohort study in Spain by Macias and colleagues mortality attributed to HCV infection was increasing, but AIDS-related illnesses were still the most common cause of death in the HAART era. Differences in patient populations, HAART regimens, and adherence to the regimens may have contributed to the different results among these cohorts.

In studies to date, factors that influence the response of HCV to antiviral therapy in HIV-coinfected patients include CD4+ cell count, HCV genotype, HCV viral load, and the presence of cirrhosis. Dr Sherman proposed that these factors argued for earlier treatment of HCV infection in HIV disease. In a small pilot study of interferon alfa (IFN-□) plus ribavirin by Bochet and colleagues (Abstract 574), the baseline HCV RNA level was the greatest predictor of response. In this study, 18% of patients had HCV RNA suppression 6 months after the discontinuation of 6 to 12 months of therapy.

The high prevalence of HCV infection, the accelerated course of HCV infection in the presence of HIV infection, and the increasing mortality associated with chronic HCV infection underscore the urgency for developing new HCV therapies. Dr Sherman noted that interleukins 2 and 10, protease and helicase inhibitors, and antisense compounds are all under development or are already in clinical trials. Pegylated IFN-□ was recently approved by the US Food and Drug Administration.

Hepatitis B Coinfection

Treatment with lamivudine decreases the replication of hepatitis B virus (HBV), but drug resistance can be identified in 50% of patients treated for 2 years and in 90% treated for 4 years. Some of the most exciting data presented at the Conference were the results of a trial that evaluated the efficacy of adefovir in HIV-infected patients in whom lamivudine treatment for hepatitis B was failing (Benhamou et al, Abstract 36). At study entry all 35 subjects had detectable HBV DNA and the M550V or M550I mutation in the HBV DNA polymerase. Treatment with adefovir 10 mg/d produced a mean decrease in the HBV DNA level of 4 $\log_{10}$ copies/mL at 32 weeks. Three subjects who were positive for hepatitis B early antigen have become negative for it during the course of this ongoing study. No changes in renal function were observed, and no patients dropped out because of adverse effects related to adefovir. For the treatment of hepatitis B, the therapeutic index of adefovir appears favorable, and the results of additional, larger efficacy studies are eagerly awaited.

Emtricitabine is another antiviral drug that also has activity against HBV. In a randomized phase 2 study (Rousseau et al, Abstract 559) of emtricitabine 25, 100, or 200 mg/d, the 200 mg dose produced the greatest reduction in HBV DNA levels (3.2 $\log_{10}$ copies/mL). Sixty-four percent of patients taking this dose had undetectable HBV DNA levels after 36 weeks of treatment. The compound also has promising activity against HIV (Van Der Horst et al, Abstract 18) at the 200 mg dose selected for development for hepatitis B treatment.

Management of Antiretroviral Therapy

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The 8th Conference on Retroviruses and Opportunistic Infections this year again presented a forum for a comprehensive update on the current status of the field of antiretroviral therapy. Dominant themes were the initiation of therapy, approaches to virologic failure, simplification of regimens, strategic approaches to management, pharmacokinetic and pharmacodynamic considerations, new agents, novel combinations, and drug resistance. New research in these areas was presented on the backdrop of the publication of the revised Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents (available at http://www.hivatis.org), sponsored by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation. The updated guidelines formalized a conservative swing in the approach to initiating treatment. An important new subtext to the meeting was that of improving access to care in the developing world. The Conference opened with keynote lectures by Drs Kevin DeCock ("Heterogeneity and Public Health in the Global HIV/AIDS Epidemic") and Jeffrey D. Sachs ("From Talk to Action in Fighting AIDS in Developing Countries"), and the final symposium on advances in antiretroviral chemotherapeutics closed on this same note, with Dr Anne-Valérie Kaninda's talk on "The Access Challenge: AIDS Treatment in Resource-Limited Settings." The reader is encouraged to listen to these talks on the Conference Web site (http://www.retroconference.org). They provide an important perspective on the global challenge of translating the advances reported at this meeting into meaningful health improvements for all HIV-infected persons.

Preclinical Investigational Agents

Data were presented on investigational compounds that demonstrate promising preclinical antiviral and pharmacokinetic properties.

Protease Inhibitors

DPC 681, DPC 684, and TMC126. The in vitro activities of several second-generation HIV protease inhibitors were reported, including those of DPC 681, DPC 684 (Erickson-Viitanen et al, Abstract 11), and TMC126 (Erickson et al, Abstract 12). Their antiviral activity is typified by increased potency, especially against viral isolates that are resistant to the currently available protease inhibitors. DPC 681 and DPC 684 are peptidomimetic compounds with 90% inhibitory concentration (IC_{90}) values for wild-type HIV-1 in the range of 4 to 8 nmol/L. These agents retain activity against more-divergent nonclade B strains. Moreover, drug-resistant chimeric viruses recombined from clinical isolates of patients in whom the current generation of protease inhibitors are failing and that harbor 6 or 7 mutations at positions 10, 63, 71, 82, 84, and 90 demonstrate only a modest 3- to 6-fold reduced susceptibility to DPC 681 and DPC 684. The investigational protease inhibitor TMC126 also shows activity at subnanomolar concentration against isolates that are resistant to the current agents. This protease inhibitor has protein-binding characteristics similar to those of ritonavir (2- to 5-fold effect on the 50% inhibitory concentration [IC_{50}] value) and satisfactory oral bioavailability. Approximately 95% of a panel of multidrug-resistant clinical isolates carrying up to 28 mutations in the protease gene remained susceptible to TMC126.

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Reverse Transcriptase Inhibitors

ACH-126,443. The initial preclinical data on several reverse transcriptase inhibitors of both the nucleoside and the nonnucleoside analogue class were presented. As with investigational agents in other classes, emphasis has been placed on developing compounds that lack intra- or multiclass cross-resistance with the currently available inhibitors. For example, Dunkle and colleagues (Abstract 303) reported on the in vitro activity of ACH-126,443 (β-L-Fd4C), an L-nucleoside analogue with a broad spectrum of activity that includes both HIV and hepatitis B virus (HBV). This compound is activated by cytoplasmic cytidine kinase to a triphosphate form with a half-life of more than 8 hours, and therefore likely would support a daily dosing schedule. In addition, this compound has minimal mitochondrial toxicity and remains active against nucleoside reverse transcriptase inhibitor (nRTI)–resistant HIV-1 strains carrying the M184V mutation with or without the T215Y, Q151M, and insert 69S mutations as well as HBV YMDD mutants.

DAPD/DXG. The pharmacokinetic characteristics of DAPD and its active metabolite, DXG, were presented by Wang and colleagues (Abstract 752). Significant findings were that DAPD is rapidly absorbed and metabolized to DXG with the plasma DXG concentrations reaching levels 3- to 12-fold higher than those of DAPD and having a plasma half-life of 7 to 9 hours. The resulting plasma DXG levels are higher than the in vitro IC_{50} value over the entire dosing interval at doses of between 100 and 500 mg twice a day. The investigators found no significant differences in the plasma pharmacokinetics in treatment-naive and treatment-experienced patients. In order to mechanistically explain the selectivity and lack of cross-resistance of DXG for HIV-1, Feng and colleagues (Abstract 306) showed that DXG triphosphate is a poor substrate for human DNA polymerases □ and □ and is incorporated

113 times less efficiently by DNA polymerase □ The efficiency of DXG triphosphate incorporation by HIV-1 reverse transcriptase was unaffected by the presence of zidovudine or lamivudine resistance mutations.

4'-Ethynyl Nucleoside Analogues. The in vitro activity of a series of 4'-ethynyl nucleoside analogues was reported by Kodama and colleagues (Abstract 305). As with other investigational nucleoside analogues, these compounds are distinguished by their spectrum of activity, which includes various drug-resistant HIV-1 clones including those that contain the M41L/T215Y mutations, the T69S-S-G insertion, L74V, K65R, and the Q151M resistance complex. The leading compounds in this group include 4'-E-2'-deoxycytidine, 4'-E-2'-deoxyadenosine, and 4'-E-2'-deoxyribosyl diaminopurine.

TMC120. Further in vitro data on TMC120 (R147681), a leading dianilino-pyrimidine compound that has entered phase 1-2 clinical trials, was presented by De Bethune and colleagues (Abstract 304). As reported at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy last year, this compound has potent activity against both wild-type HIV-1 and strains carrying key mutations and dual mutations that confer high-level resistance to nevirapine, delavirdine, and efavirenz. This includes isolates with mutations at codons 100, 103, 106, 181, 188, and 190. The potency of TMC120 is unaffected by incubation with □$_1$-acid glycoprotein and is affected moderately by human serum albumin (18-fold increase in IC_{50}). After incubation for 2 hours with human liver microsomes, it remains relatively stable, with approximately 35% degradation, indicating its potential metabolic profile in vivo.

The results of a phase 1-2 trial that compared TMC120 50 or 100 mg orally twice a day with placebo in 43 antiretroviral-naive subjects were reported by Gruzdev and colleagues (Abstract 13). The patients had baseline plasma HIV-1 RNA and CD4+ cell counts of approximately 4.5 $\log_{10}$ copies/mL and 519 to 649/μL. The short-term, 7-day virologic response was characterized by a mean decrease of 1.44 and 1.51 $\log_{10}$ copies/mL, respectively, in the 2 TMC120 study arms and of 0.17 $\log_{10}$ copies/mL with placebo (intent-to-treat [ITT] analysis, $P < .001$). The CD4+ cell counts increased by a statistically significant 120/μL more with TMC120 than with placebo. Adequate trough levels were obtained with both doses (104 and 208 ng/mL, respectively). Headache was the most common adverse effect, occurring in 13% of the subjects in the TMC120 100-mg arm.

Full text of all Conference abstracts, as well as selected posters and audio recordings and slide presentations of symposia and lectures, are available on the official Conference Web site, www.retroconference.org.

HIV-1 Attachment/Entry Inhibitors

Data on a variety of other novel agents that target 1 or more novel viral replicatory functions were presented. Shu and colleagues (Abstract 309) reported on a series of small-molecule inhibitors of HIV-1 cell entry. These compounds inhibit R5 and/or X4 virus-associated cell fusion. Compound #17, for example, inhibited both virus types at concentrations of approximately 1 μg/mL and had a favorable cell-toxicity profile, with minimal effects at concentrations greater than 60 μg/mL. Similarly, acknowledging that R5 or X4 coreceptor–blocking agents could lead to the emergence of coreceptor switch variants, Picchio and colleagues (Abstract 311) demonstrated that combined CCR5 (NNY-RANTES) and CXCR4 (AMD3100) inhibitors completely blocked infection with R5 virus while preventing the emergence of CXCR4-using variants in a hu-PBL-SCID murine model.

Data were also presented on 2 compounds that appear to inhibit several HIV-1 replicatory functions, including cell entry. The 4-methyl dicamphanoyl khellactone (4-methyl DCK) compound inhibits all HIV-1 subtypes with potency similar to that of zidovudine and a selectivity index of greater than 1000 in an XTT cell viability assay (Wild et al, Abstract 302). Its antiviral activity is unaffected by incubation with human serum, and it has synergy with zidovudine and retains activity against zidovudine-resistant strains. Alfano and colleagues (Abstract 313) presented in vitro data on the binding subunit of pertussis toxin (PTX-B). This compound also appears to exert inhibitory effects at several viral replicatory steps, including the inhibition of R5 virus entry and the inhibition of X4 reactivation in chronically infected U1 cells that have been stimulated with tumor necrosis factor □ or interleukin 6.

Trials of Initial Therapy in Antiretroviral-Naive Patients

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

Extended Follow-Up of Previously Reported Trials

START Observational Study. Long-term virologic and immunologic responses with additional follow-up safety data through 192 weeks were evaluated in the START Observational Study (Murphy et al, Abstract 314), which enrolled subjects who had participated in the START I and II trials and who remained on their original study drug regimens. The START I and II comparative trials were multicenter randomized observational 48-week studies that evaluated the efficacy and safety of 3 dual–nRTI-based regimens used in combination with a protease inhibitor, indinavir, in treatment-naive patients with pretreatment HIV RNA levels of 5000 copies/mL or greater and CD4+ cell counts of 200/μL or greater. The original START trials compared stavudine/lamivudine/indinavir (n = 101; START I) and stavudine/didanosine (chewable tablets)/indinavir (n = 102; START II) with zidovudine/lamivudine/indinavir (n = 206; START I and II). The durability of virologic suppression (<500 copies/mL) during the observational study was similar in the 3 treatment arms through week 72: HIV RNA levels of less than 500 copies/mL were maintained in 35 (80%) of 44, 24 (69%) of 35, and 48 (72%) of 67 of the subjects in the stavudine/lamivudine/indinavir, stavudine/didanosine/indinavir, and zidovudine/lamivudine/indinavir arms, respectively. The change from the baseline CD4+ cell count was comparable among the 3 study arms at week 72: the calculated CD4+ DAVG median values (time-weighted average CD4+ cell count minus baseline CD4+ cell count values) were 180, 188, and 177 cells/μL, respectively.

Owing to the small size of the cohort beyond year 2, statistically significant differences in the study end points emerged at later times. Eighteen (20%) of 91 subjects in the observational study prematurely discontinued participation. At week 144, 11 (55%) of 20, 2 (14%) of 14, and 12 (44%) of 27 of the subjects in the stavudine/lamivudine/indinavir, stavudine/didanosine/indinavir, and zidovudine/lamivudine/indinavir arms, respectively, had HIV RNA levels of less than 500

copies/mL (P = .03 for stavudine/lamivudine/indinavir vs stavudine/didanosine/indinavir, Fisher exact test). The calculated CD4+ cell count DAVG values at week 144 were 266 (n = 10), 107 (n = 3), and 250/µL (n = 13), respectively (P = .028 for stavudine/lamivudine/indinavir vs stavudine/didanosine/indinavir, Wilcoxon signed rank test). There were no unexpected adverse events in the 3 study arms, and the study drugs were generally well tolerated. Paresthesias, rash, and abnormal liver function test results were more frequently reported in the stavudine/didanosine/indinavir group.

DMP 006 Study. Time to virologic failure of the initial antiretroviral therapy regimen, according to Kaplan-Meier estimates, was evaluated in 1266 HIV-infected treatment-naive subjects who were randomized in the DMP 006 multicenter open-label trial. The trial compared the efficacy of efavirenz/zidovudine/lamivudine, indinavir/zidovudine/lamivudine, and efavirenz/indinavir (Levy et al, Abstract 325). The mean baseline CD4+ cell count and viral load were 341/µL and 60,250 copies/mL, respectively. Time to virologic failure was defined as a confirmed plasma viral load of greater than 50 copies/mL. In this analysis, discontinuations and Centers for Disease Control and Prevention (CDC) category C events were censored. Viral suppression to less than 50 copies/mL was never achieved in 8% of the 422 subjects in the efavirenz/zidovudine/lamivudine arm. The viral rebound rates in the efavirenz/zidovudine/lamivudine arm were 8% in year 1, 7% in year 2, and 3.5% in year 3. In the efavirenz/indinavir and indinavir/zidovudine/lamivudine arms HIV-1 RNA levels of less than 50 copies/mL were never achieved in 14% and 12%, respectively. Nineteen percent and 7% of the subjects in the efavirenz/indinavir arm, respectively, experienced virologic failure during year 1 and year 2; the corresponding rates were 15% and 8% in the indinavir/zidovudine/lamivudine arm. At year 3 (week 144) the rates of virologic failure in the efavirenz/indinavir and the indinavir/zidovudine/lamivudine arms were 2.5% and 12%, respectively.

In a subset with CD4+ cell counts of less than 200/µL, 76% (n = 107), 41% (n = 120), and 54% (n = 104) of the subjects in the efavirenz/zidovudine/lamivudine, efavirenz/indinavir, and zidovudine/lamivudine/indinavir arms, respectively, had HIV-1 RNA levels of less than 50 copies/mL at week 96 (efavirenz/zidovudine/lamivudine vs indinavir/zidovudine/lamivudine, P = 0.092; efavirenz/zidovudine/lamivudine vs efavirenz/indinavir, P < .001). The time to virologic failure was longer when therapy was initiated at CD4+ cell counts of greater than 200/µL; the virologic failure rates were independent of baseline CD4+ cell count with efavirenz/zidovudine/lamivudine. Based on the virologic failure rates observed in the efavirenz/zidovudine/lamivudine arm during the first 2 years of DMP 006, the median time to virologic failure with this initial antiretroviral regimen is expected to exceed 6 years.

Protease Inhibitor–Sparing Regimens: COMBINE Study. A number of recent clinical trials have compared the virologic efficacy and long-term adverse-event profiles of single protease inhibitor–based combination regimens with those of nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens.

Podzamczer and colleagues (Abstract 327) presented the 36-week results of the COMBINE study, a multicenter open-label randomized comparative trial that evaluated the virologic efficacy and safety of fixed-dose lamivudine/zidovudine plus nelfinavir or nevirapine in 142 HIV-infected treatment-naive patients. Patients with median baseline viral loads of 4.81 and 4.77 $\log_{10}$ copies/mL and median CD4+ cell counts of 351 and 361/µL, respectively, were randomized to fixed-dose lamivudine/zidovudine plus nelfinavir 1250 mg twice daily (n = 70); or fixed-dose lamivudine/zidovudine plus nevirapine 200 mg twice daily (n = 72). The primary outcome measure was the proportion of subjects in whom viral suppression to less than 200 copies/mL at 48 weeks was achieved.

By using ITT analysis (missing data = failure [M = F]), HIV-1 RNA levels of less than 200 copies/mL and less than 20 copies/mL, respectively, were achieved in 70.8% and 66.7% of the subjects in the nevirapine-containing arm at 36 weeks compared to 55.7% and 38.6% of subjects, respectively, in the nelfinavir-containing arm (HIV-1 RNA <200 copies/mL; P = .06; HIV RNA <20 copies/mL; P < .001). In a subset with baseline HIV-1 RNA levels greater than 100,000 copies/mL, viral suppression of less than 20 copies/mL at 36 weeks was achieved in 13 (61.9%) of 21 patients in the nevirapine-containing arm and in 4 (15.4%) of 26 patients in the nelfinavir-containing arm (ITT; P = .001). The nelfinavir-containing arm had poorer adherence to the study drug regimen than did the nevirapine-containing arm (59% vs 75%; P = .03). Low trough levels of nelfinavir were not seen in the subjects in the nelfinavir-containing arm in whom there was virologic failure. Diarrhea that resulted in discontinuation of study medications was more frequent in the nelfinavir-containing arm (14%) than in the nevirapine-containing arm (1%; P = .004). Anemia and neutropenia that resulted in study drug discontinuation (only zidovudine was discontinued and switched to stavudine) occurred more often in the nevirapine-containing arm than in the nelfinavir-containing arm (P = .06).

Initial Combination Therapy With Three Drug Classes

The efficacy and tolerability of nevirapine was compared with those of lamivudine in combination with stavudine and indinavir in 145 HIV-infected (antiretroviral-naive, n = 115; zidovudine- or didanosine-exposed, n = 30) patients with mean baseline HIV-1 RNA levels and CD4+ cell counts of 5.15 $\log_{10}$ copies/mL and 359/µL, respectively. Launay and colleagues (Abstract 326) presented the week-72 results. In an ITT analysis, 81% and 62% of the subjects in the lamivudine- and nevirapine-containing arms, respectively, had HIV-1 RNA levels of less than 20 copies/mL at 72 weeks (P = .02). Both arms sustained similar increases in CD4+ cell counts (239 and 199/µL in the lamivudine and nevirapine arms, respectively). The nevirapine arm had higher discontinuation rates than the lamivudine arm (44% vs 25%; P = .008). In the nevirapine arm, 10 patients had rash of a grade higher than 2 and 7 patients had hepatitis of a grade higher than 2. In this trial, a nevirapine-containing regimen did not provide viral suppression in NNRTI-naive subjects that was greater than that with dual-nRTI plus indinavir therapy.

Investigational nRTI Drugs

Emtricitabine is an investigational nRTI with potent in vitro activity against HIV 4 to 10 times greater than that of lamivudine. Van Der Horst and colleagues (Abstract 18) presented the results of 2 randomized controlled equivalence trials of lamivudine 150 mg twice daily compared with emtricitabine 200 mg once daily in triple-therapy regimens. The emtricitabine-303 trial was a randomized open-label switch study in HIV-infected patients who had been treated with a lamivudine–containing triple regimen for 12 weeks or longer and had HIV-1 RNA levels of less than 400 copies/mL. After randomization, patients (n = 440) were switched to emtricitabine or continued

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

Study (Abstract No.)	Regimen/Study Arm	No. of Patients	Weeks of Therapy	Baseline Plasma HIV-1 RNA (copies/mL)
COMBINE (327)	1. Nevirapine/ zidovudine/lamivudine	72	36	4.77 $\log_{10}$ (mean)
	2. Nelfinavir/ zidovudine/lamivudine	70		4.81 $\log_{10}$
Initial Antiretroviral Therapy: 3 Drug Classes (326)	1. Nevirapine/ stavudine/indinavir	145 (total in 2 arms)	72	5.15 $\log_{10}$ (overall mean)
	2. Lamivudine/ stavudine/indinavir			
FTC 303 Switch Study (18)	1. Continue lamivudine-containing regimen	440 total in 2 arms; randomized to emtricitabine/lamivudine vs lamivudine in 2:1 ratio	48	≤400
	2. Switch to emtricitabine-containing regimen			
FTC 302 (18)	1. Emtricitabine/stavudine plus nevirapine or efavirenz	468 (total in both arms)	48	40,000 (overall median)
	2. Lamivudine/stavudine plus nevirapine or efavirenz			Screening HIV RNA <100,000: nevirapine stratum (n = 385); ≥100,000: efavirenz stratum (n = 83).
Didanosine-EC qd vs Didanosine qd (318)	1. Didanosine-EC/stavudine/ nelfinavir	72	48	4.71 $\log_{10}$ (median)
	2. Didanosine/ stavudine/nelfinavir	66		4.63 $\log_{10}$ (median)
A1454-152 (319)	1. Didanosine-EC/stavudine/ nelfinavir	258	48	49,000 (mean)
	2. Fixed-dose zidovudine/lamivudine plus nelfinavir	253		55,000
Fixed-Dose Zidovudine/ Lamivudine/Abacavir (315)	1. Switch to fixed-dose zidovudine/lamivudine/abacavir bid plus stable background treatment (PI or NNRTI)	97	24	1.75 $\log_{10}$ (median)
	2. Continue fixed-dose zidovudine/lamivudine plus abacavir plus stable background treatment (PI or NNRTI)	98		1.78 $\log_{10}$

ITT indicates intent-to-treat; M = F indicates missing data equals failure; CI indicates confidence interval; AST indicates aspartate aminotransferase; ALT indicates nonnucleoside reverse transcriptase inhibitor; HAART indicates highly active antiretroviral therapy; sgc indicates soft gel capsule; hgc indicates hard gel capsule;

Baseline CD4+ Count (cells/μL)	Plasma HIV-1 RNA Effect (copies/mL)	CD4+ Count Change (cells/μL)	Comments
361 (mean)	70.8% <200 nevirapine vs nelfinavir: *P* = .06 66.7% <20 nevirapine vs nelfinavir: *P* < .001 (ITT analysis)	+116	In patients with baseline HIV-1 RNA >5 $\log_{10}$ copies/mL, the nevirapine-containing arm achieved superior viral load suppression of <20 copies/mL (*P* = .001).
351 (mean)	55.7% <200, 38.6% <20 (ITT analysis)	+172	
359 (overall mean)	62% <20 (ITT analysis; M = F) 81% <20	+199 (median) +239 (median)	Lamivudine arm achieved superior viral load suppression (*P* = .02). Nevirapine arm had higher discontinuation rate than lamivudine arm (44% vs 25%; *P* = .008). Nevirapine arm had grade 2 or higher hepatitis (n = 7) and rash (n = 10).
N/A	75% <50 (ITT analysis; M = F) 68% <50	N/A	95% CI was –4.1 to 3.6 for difference between emtricitabine and lamivudine in proportion of virologic failure (HIV-1 RNA >400 copies/mL on 2 occasions) at week 48. Only mild to moderate adverse events reported in both arms.
N/A	61% <50 (ITT analysis; M = F) 65% <50	N/A	Rates of virologic failure (defined as HIV-1 RNA >400 copies/mL on 2 occasions) were 12% in the emtricitabine arm vs 6% in the lamivudine arm. Grade 3 or 4 AST/ALT elevations were seen in 17% of patients in nevirapine-stratum vs none in efavirenz-stratum: 62% were HBsAg+ and 30% had hepatitis C. Incidence was 20% in women vs 12% in men.
382 (median)	–2.62 $\log_{10}$ (median decline from baseline)	+100 (mean)	2 patients (3%) in didanosine arm had grade 3 or 4 elevated lipase levels vs 0 in the didanosine-EC arm. No reports of pancreatitis in either arm.
363 (median)	–2.35 $\log_{10}$	+120 (mean)	
411 (mean)	57% <400 (ITT analysis; M = F)	+100 (median)	No significant difference in proportion of patients with HIV-1 RNA <50 copies/mL. Frequency of adverse events similar in both arms.
411 (mean)	55% <400	+147 (median)	
637 (median)	99% <400, 88% <50 (ITT analysis)	+58 (median)	Switch to fixed-dose zidovudine/lamivudine/abacavir as effective as continuing fixed-dose zidovudine/lamivudine plus abacavir in maintaining viral load suppression through week 24. No abacavir hypersensitivity.
535.5	92% <400, 78% <50	+61.5	

(table continued on next page)

alanine aminotransferase; didanosine-EC indicates didanosine enteric-coated formulation; PI indicates protease inhibitor; NNRTI indicates
NC = F indicates noncomplete equals failure; HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein; NS indicates not significant.

Table **1.** Trials in Antiretroviral-Naive Subjects *(continued from page 17)*

Study (Abstract No.)	Regimen/Study Arm	No. of Patients	Weeks of Therapy	Baseline Plasma HIV-1 RNA (copies/mL)
AL30002 (316)	1. Switch to zidovudine/lamivudine/abacavir	106	24	<50
	2. Continue same stable HAART regimen (PI- or NNRTI-based)	102		
M98-863 (329)	1. Lopinavir/ritonavir plus stavudine/lamivudine	326	48	Screening viral load: >400
	2. Nelfinavir/stavudine/lamivudine (lopinavir/ritonavir and nelfinavir: double-blind)	327		
Delavirdine plus Saquinavir sgc Combination Therapy (331)	1. Saquinavir sgc 1400 mg bid/ lamivudine/delavirdine 600 mg bid	24	24	4.7–4.9 $\log_{10}$ (overall mean)
	2. Saquinavir sgc 1000 mg tid/ lamivudine/delavirdine 400 mg tid	24		
	3. Saquinavir sgc 1200 mg tid/ lamivudine/zidovudine 200 mg tid	24		
	4. Saquinavir sgc 1400 mg bid/ lamivudine/delavirdine 600 mg bid/ zidovudine 200 mg bid	24		
Women First Trial (330)	1. Nelfinavir plus saquinavir hgc bid/stavudine/lamivudine	33	48	4.86 $\log_{10}$ (median)
	2. Nelfinavir plus saquinavir tid/ stavudine/lamivudine	35 (women only)		4.66 $\log_{10}$
A1424-007 Study (15)	BMS-232632 vs nelfinavir monotherapy (2 weeks); then	Stage I (n = 98)	48	4.8 $\log_{10}$
	1. BMS-232632 (200 mg)/ didanosine/stavudine	Stage II (n = 322)	24	4.71 $\log_{10}$
	2. BMS-232632 (400 mg)/ didanosine/stavudine			
	3. BMS-232632 (500 mg)/ didanosine/stavudine			
	4. Nelfinavir/stavudine/didanosine stage I and stage II			
APV20001: GW433908-Amprenavir Prodrug (333)	1. GW433908 1395 mg/ abacavir/lamivudine	28	28 days	4.75 $\log_{10}$ (median)
	2. GW433908 1860 mg/ abacavir/lamivudine	29		4.52 $\log_{10}$
	3.Amprenavir/abacavir/lamivudine	28		4.58 $\log_{10}$

ITT indicates intent-to-treat; M = F indicates missing data equals failure; CI indicates confidence interval; AST indicates aspartate aminotransferase; ALT indicates alanine aminotransferase; didanosine-EC indicates didanosine enteric-coated formulation; PI indicates protease inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; HAART indicates highly active antiretroviral therapy; sgc indicates soft gel capsule; hgc indicates hard gel capsule; NC = F indicates noncomplete equals failure; HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein; NS indicates not significant.

Baseline CD4+ Count (cells/μL)	Plasma HIV-1 RNA Effect (copies/mL)	CD4+ Count Change (cells/μL)	Comments
N/A	20% virologic failure (defined as HIV-1 RNA >400 copies/mL on 2 occasions) 17% virologic failure	N/A	Adverse events (12% in zidovudine/lamivudine/abacavir arm and 13% in HAART arm) most frequent cause of study discontinuations. Significant reductions in fasting cholesterol ($P < .001$) and triglyceride ($P = .003$) levels were seen in zidovudine/lamivudine/abacavir arm.
N/A	75% <400 (ITT analysis; M = F) 63% <400	N/A	Among patients with HIV-1 RNA >50 copies/mL at week 24, 88% of patients in lopinavir/ritonavir arm achieved HIV RNA <50 copies/mL during weeks 32–48 vs 41% in nelfinavir arm ($P < .001$)
224–280 (overall mean)	83% <400, 63% <50 48% <400, 43% <50 63% <400, 50% <50 76% <400, 64% <50 (ITT analysis; M = F)	N/A	Group 1 had superior viral suppression (<400 copies/mL) vs group 2 ($P = .0127$). Group 4 had superior viral suppression (<400 copies/mL) vs group 2 ($P = .0438$). Based on inferior viral suppression rates in tid dosing in groups 2 and 3, bid regimens preferred. Delavirdine-associated rash in <5%.
294 (median) 264.5	60.6% <400* 54.5% <50** (ITT analysis; NC = F) 44.8% <400 32.3% <50 *bid vs tid ($P = .214$) **bid vs tid ($P = .07$)	+239.89 (mean) +196.34	Study arms had similar virologic efficacy. Nelfinavir/saquinavir bid and tid regimens were well tolerated. Modest increase in nonfasting cholesterol levels were observed, but not in triglycerides.
	BMS-232632 arms: 2.3–2.8 $\log_{10}$ reduction (median) BMS-232632 arms: 2.5–2.6 $\log_{10}$ reduction BMS-232632 arms (stage II): 65%–68% <400 vs nelfinavir arm: 63% <400 (ITT analysis)	+100 (median)	Stage II: 30%–35% of patients in BMS-232632 (400 mg and 500 mg) arms achieved HIV-1 RNA <50 copies/mL (ITT). 74% grade 3 or 4 elevations in bilirubin levels seen in BMS-232632 arms. All BMS-232632 arms sustained a rise in HDL cholesterol levels; no change in LDL cholesterol levels seen.
245 (median) 348 177	–1.97 $\log_{10}$ (median) –1.88 $\log_{10}$ –1.98 $\log_{10}$	+111 (median) +106 +92	GW433908 achieves similar virologic efficacy (~ 2 $\log_{10}$ HIV-1 RNA decline over 28 days) vs amprevanir-containing regimen. Safety of GW433908 is comparable to safety of amprenavir; improved formulation allows for reduced daily pill burden.

(table continued on next page)

Table **1.** Trials in Antiretroviral-Naive Subjects *(continued from page 19)*

Study (Abstract No.)	Regimen/Study Arm	No. of Patients	Weeks of Therapy	Baseline Plasma HIV-1 RNA (copies/mL)
NICE Study (334)	1. Indinavir tid plus 2 nRTIs	84	24	Screening HIV-1 RNA <400
	2. Indinavir 400 mg/ ritonavir 100 mg bid plus 2 nRTIs	345		
Merck 103/104: Once-Daily Indinavir/Ritonavir (336)	Indinavir 1200 mg/ritonavir 100 mg qd plus stavudine/ritonavir bid	40	24	4.91 $\log_{10}$ (median)
APV20001 (332)	1. Amprenavir 1200 mg/ritonavir 100 mg qd plus abacavir/lamivudine bid	15	12	4.85 $\log_{10}$ (median)
	2. Amprenavir 600 mg/ritonavir 100 mg bid plus abacavir/lamivudine bid	21		4.80 $\log_{10}$
COLA4005 (317)	1. Lamivudine 150 mg bid plus stavudine plus PI (nelfinavir or indinavir)	42	24	49 (median)
	2. Lamivudine 300 mg qd plus stavudine plus PI	37		49
ANRS 091 (321)	Once-daily regimen: emtricitabine 200 mg plus didanosine 400 mg plus efavirenz 600 mg	40	64	4.77 $\log_{10}$ (median)
Once-Daily Regimen (320)	Once-daily regimen: didanosine 300 mg/lamivudine 300 mg/efavirenz 600 mg	75	48	123,000 (median)

ITT indicates intent-to-treat; M = F indicates missing data equals failure; CI indicates confidence interval; AST indicates aspartate aminotransferase; ALT indicates nonnucleoside reverse transcriptase inhibitor; HAART indicates highly active antiretroviral therapy; sgc indicates soft gel capsule; hgc indicates hard gel capsule; significant.

lamivudine in a 2:1 ratio. At week 48 (ITT; M = F) the proportions of patients with continued viral suppression to less than 50 copies/mL were 68% and 75% in the emtricitabine and lamivudine arms, respectively. The 95% confidence interval (CI) for the difference between emtricitabine and lamivudine in the proportion of patients in whom there was virologic failure (HIV-1 RNA >400 copies/mL on 2 consecutive occasions) was 4.1 to 3.6 at week 48. Emtricitabine and lamivudine were well tolerated with only mild to moderate adverse events in both treatment arms.

Emtricitabine-302 was a randomized, double-blind trial conducted in South Africa in antiretroviral therapy–naive HIV-infected patients. It compared emtricitabine (300 mg qd) to lamivudine (150 mg bid) in combination with stavudine plus nevirapine (nevirapine stratum: screening HIV-1 RNA <100,000 copies/mL) or efavirenz (efavirenz stratum: screening HIV-1 RNA >100,000 copies/mL). A total of 468 patients with median baseline HIV-1 RNA of 40,000 copies/mL were enrolled. At week 48 (ITT analysis; M = F), the proportions of patients with HIV RNA levels less than 50 copies/mL were 61% and 65% in the emtricitabine and lamivudine arms, respectively. Rates of virologic failure at week 48 were 12% in the emtricitabine arm compared with 6% in the lamivudine arm. These 2 trials supported the equivalent antiviral efficacy and safety of once-daily emtricitabine compared to twice-daily lamivudine. In the emtricitabine-302 study, grade 3 or 4 aspartate aminotransferase/alanine aminotransferase elevations were observed in 17% of patients in the nevirapine stratum (n = 385) versus none in the efavirenz stratum (n = 83) (Bartlett et al, Abstract 19). Of the patients who developed grade 3 or 4 transaminitis, 36% had gastrointestinal symptoms, 34% had grade 3 to 4 serum bilirubin elevations, 77% of patients developed hepatotoxicity during the first 4 weeks, 62% were hepatitis surface antigen–positive, and 30% had hepatitis C. There were 2 deaths due to hepatic failure; both patients who died were receiving nevirapine/stavudine/lamivudine. There was no significant difference in development of hepatotoxicity in patients in the lamivudine versus emtricitabine arm (P = .27). The incidence of hepatotoxicity was twice as frequent in women versus men (20% women; 12% men). Based on these trial results, frequent monitoring of liver function test results during the first 4 weeks of nevirapine exposure is advised.

Trials Evaluating New Nucleoside Analogue Formulations

Didanosine Enteric Coated Formulation. Although buffered formulations of didanosine chewable tablets have demonstrated virologic efficacy in a number of clinical trials, this formulation is frequently associated with adverse gastrointestinal effects that limit its tolerability. A new encapsulated, buffer-free formulation of enteric-coated beadlets (didanosine-EC) was developed to

Baseline CD4+ Count (cells/μL)	Plasma HIV-1 RNA Effect (copies/mL)	CD4+ Count Change (cells/μL)	Comments
544 (mean)	88% <400	CD4+ counts stable (P = NS)	12% of patients in indinavir/ritonavir arm had elevated fasting triglyceride levels vs 3% in indinavir arm (P = .054). 1 case of renal stones in indinavir tid arm.
571	92% <400		
329 (median)	71.8% <400, 53.8% <50 (ITT analysis; NC = F)	+157 (median)	40% patients had grade 2 or 3 adverse events; 1 case of renal stones. Modest increases in fasting triglyceride and cholesterol levels at week 24.
182 (median)	100% <400	+161 (median)	Drug regimens were well tolerated. Grade 2 cholesterol levels seen in amprenavir/ritonavir arms: bid (25%) and qd (13%). Grade 2 triglyceride levels only in amprenavir/ritonavir bid arm.
348	72% <400	+215	
532 (median)	90% <400 (ITT analysis; M = F)		Regimens had similar virologic efficacy and were well tolerated, with <5% adverse events in each arm.
514	95% <400		
373 (median)	90% <400 (ITT analysis)	+219 (median)	In a subset with baseline HIV-1 RNA >100,000 copies/mL, 88% (7/8) had suppression <400 copies/mL at week 24. 10% of patients had rash during the first 24 weeks.
251 (median)	77% <50 (ITT anlaysis), 93.6% <50 (as-treated analysis)	+449 (median)	In a subset of patients with baseline HIV-1 RNA >100,000 copies/mL, 76.3% had <50 copies/mL at week 48. 4 patients had virologic failure (HIV-1 RNA >500 copies/mL); 4 had M184V mutation and 1 had K103N mutation.

alanine aminotransferase; didanosine-EC indicates didanosine enteric-coated formulation; PI indicates protease inhibitor; NNRTI indicates NC = F indicates noncomplete equals failure; HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein; NS indicates not

improve tolerability and to eliminate unfavorable drug interactions when concurrently administered with drugs such as indinavir and ketoconazole.

Schrader and colleagues (Abstract 318) reported the week-48 results of a multicenter, randomized, open-label trial that compared the antiviral activity of didanosine-EC with didanosine when used in combination with stavudine and nelfinavir in 138 treatment-naive HIV-infected subjects. Median baseline HIV-1 RNA levels and CD4+ cell counts were 4.71 and 4.63 $\log_{10}$ copies/mL and 382 and 363/μL, respectively, in the didanosine-EC (n = 72) and didanosine tablet (n = 66) arms. Both study arms sustained similar declines in HIV-1 RNA levels from baseline to week 48: □2.62 $\log_{10}$ copies/mL in the didanosine-EC arm versus □2.35 $\log_{10}$ copies/mL in the didanosine tablet arm. Mean CD4+ cell count change from baseline to week 48 was similar for both study arms (100–120/μL), with no significant difference observed. The didanosine tablet arm reported a grade 3 or 4 elevated serum lipase in 2 (3%) of subjects, whereas the didanosine-EC arm had no elevation. There were no reports of pancreatitis in either arm, and no significant differences in adverse events between the 2 study arms were identified.

The week-48 results of the AI454-152 multicenter, open-label, randomized trial were presented by Gathe and colleagues. (Abstract 319). The antiviral activity of once-daily didanosine-EC (400 mg) in combination with stavudine plus nelfinavir was compared to fixed-dose lamivudine/zidovudine plus nelfinavir in 511 HIV-infected, treatment-naive subjects. Mean baseline HIV-1 RNA levels were 49,000 (didanosine-EC arm; n=258) and 55,000 (lamivudine/zidovudine arm; n = 253) copies/mL; mean baseline CD4+ cell count was 411/μL in both arms. Nelfinavir was administered as 750 mg 3 times a day and taken separately from didanosine-EC. The primary end point compared the proportion of responders (defined as subjects with HIV-1 RNA level below the limit of quantification at weeks 24 and 48); dropouts were reported as failures. In the primary analysis, the proportions of subjects who achieved HIV-1 RNA less than 400 copies/mL at week 48 were similar in both study arms (57% in the didanosine-EC arm vs 55% in the lamivudine/zidovudine arm). In the HIV-1 RNA level less than 50 copies/mL analysis, there were no significant differences between the study arms in the proportion of patients who had viral suppression at week 48. Median CD4+ cell count increases at week 48 were similar in both study arms (+100/μL in the didanosine-EC arm vs +147/μL in the lamivudine/zidovudine arm). The frequency of adverse clinical and laboratory events was similar in both arms. Grade 1 to 4 peripheral neuropathy was more commonly reported in

the didanosine-EC arm (8%) compared to the lamivudine/zidovudine arm (3%), but there were no increased grade 3 or 4 peripheral neuropathy events identified in the didanosine-EC arm. Clinical pancreatitis was not reported in either arm. Diarrhea was attributed to nelfinavir exposure, and similar rates of diarrhea (21%–22%) were reported in both study arms.

Fixed-Dose Lamivudine/Zidovudine/Abacavir. Nucleoside reverse transcriptase inhibitor combination therapy regimens using fixed-dose lamivudine/zidovudine plus abacavir twice daily have conferred virologic efficacy in treatment-naive HIV-infected patients. A fixed-dose combination tablet containing zidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg with established bioequivalence to fixed-dose lamivudine/zidovudine plus abacavir was developed to provide a potent, compact antiretroviral therapy regimen with a twice-daily dosing schedule that could have a favorable impact on long-term adherence.

Fischl and colleagues (Abstract 315) presented the 24-week results of a phase 3, open-label, randomized, comparative trial that evaluated the virologic efficacy of lamivudine/zidovudine/abacavir (1 tablet bid) versus a regimen of lamivudine/zidovudine (1 tablet bid) plus abacavir 300 mg twice daily in HIV-infected patients who were previously receiving lamivudine/zidovudine plus abacavir in combination with a protease inhibitor or NNRTI for at least 16 weeks. Eligibility criteria required virologic suppression of HIV-1 RNA levels of 400 copies/mL or less and CD4+ cell counts of 200/µL or greater at study entry. A total of 195 patients with median baseline HIV-1 RNA levels and CD4+ cell counts of 1.77 $\log_{10}$ copies/mL and 571.5/µL were randomized to either continue lamivudine/zidovudine plus abacavir (n = 98) or switch to lamivudine/zidovudine/abacavir (n = 97) for 24 weeks. Subjects were stratified by current adjunctive therapy (protease inhibitor, NNRTI, or none). In an ITT analysis at 24 weeks, 99% and 88% of patients in the lamivudine/zidovudine/abacavir group achieved HIV-1 RNA levels of less than 400 and less than 50 copies/mL, respectively, compared to 92% and 78% of patients, respectively, in the lamivudine/zidovudine plus abacavir group. Similar increases in median CD4+ cell counts were observed in both study arms at week 24 (+58/µL in the lamivudine/zidovudine/abacavir arm; +62/µL in the lamivudine/zidovudine plus abacavir arm). This study demonstrated that a switch to lamivudine/zidovudine/abacavir was as effective as continuing lamivudine/zidovudine plus abacavir therapy in achieving viral load suppression through 24 weeks. The study regimens were well tolerated. No subject experienced abacavir hypersensitivity, which probably relates to the fact that all patients enrolling in the study had a prior exposure to an abacavir-containing regimen for at least 16 weeks.

Katlama and colleagues (Abstract 316) presented the week-24 results from the AZL30002 study, a phase 3, 48-week, randomized, open-label multicenter trial that compared the virologic efficacy and durability of response in subjects with viral load suppression who switched to lamivudine/zidovudine/abacavir twice daily versus subjects who remained on their current antiretroviral regimen. Eligible subjects had screening HIV-1 RNA levels below 50 copies/mL and no history of virologic failure; a minimum duration of 6 months of stable prestudy antiretroviral therapy was required and any protease inhibitor–based or NNRTI-based therapy in combination with nRTIs was allowed. Median duration of prior antiretroviral exposure was 24 to 27 months for both study arms. The majority of patients in each arm were taking 2 nRTIs plus a protease inhibitor at study entry: 62% in the lamivudine/zidovudine/abacavir arm (n = 106) and 63% in the continued highly active antiretroviral therapy (HAART) arm (n = 103). Treatment failure was defined as virologic failure (HIV RNA > 400 copies/mL on 2 consecutive occasions) or premature discontinuation of randomized treatment. At 24 weeks, the treatment failure rates were similar in both arms. Twenty percent (21/106) of patients in the lamivudine/zidovudine/abacavir arm experienced treatment failure (5 virologic failures and 16 treatment discontinuations) compared to 17% (17/103) of patients in the continued-HAART arm (1 virologic failure and 16 treatment discontinuations). The most common reason for premature study drug discontinuation was adverse events (12% and 13% in the lamivudine/zidovudine/abacavir and continued HAART arms, respectively). Possible abacavir-related hypersensitivity reactions in the lamivudine/zidovudine/abacavir group and possible manifestations of lipodystrophy syndrome in the continued-HAART arm were the most frequently reported adverse events prompting treatment discontinuation. Significant reductions in fasting cholesterol (P < .001) and triglyceride levels (P = .003) were observed at week 24 in the lamivudine/zidovudine/abacavir arm compared to the continued-HAART arm.

Trials of Protease Inhibitor–Based Therapy

Approved Protease Inhibitor Agents. King and colleagues presented the results of the M98-863 study (Abstract 329), a double-blind, randomized, multicenter trial that compared the time to achieve viral load suppression (HIV RNA <400 copies/mL and <50 copies/mL) at 48 weeks in treatment-naive HIV-infected patients with screening HIV RNA levels greater than 400 copies/mL who were randomized to lopinavir/ritonavir plus stavudine/lamivudine bid (n = 326) or nelfinavir 750 mg tid plus stavudine/lamivudine bid (n = 327). At week 48, the lopinavir/r arm demonstrated a significantly higher response rate than the nelfinavir arm in ITT analyses of the proportion of subjects with HIV RNA levels less than 400 copies/mL (75% vs 63%; P < .001) or less than 50 copies/mL (67% vs 52%; P < .001). The majority of patients achieved HIV RNA levels of less than 400 copies/mL by week 24; only 0.2% (1/592) patients required a longer time to achieve suppression. In contrast, 99 (20%) of 507 patients achieved their first HIV RNA level of less than 50 copies/mL at weeks 32 to 48. Among patients with HIV RNA levels higher than 50 copies/mL at week 24 who remained on study, more patients in the lopinavir/r arm (88%) achieved HIV RNA levels below 50 copies/mL compared to those in the nelfinavir arm (41%; P < .001). Higher baseline viral load was significantly associated with a longer time to achieve HIV RNA levels below 50 copies/mL (beyond week 24). In the lopinavir/r arm, similar proportions of patients with baseline HIV RNA levels greater than 100,000 (84%) or less than 100,000 copies/mL (85%) ultimately achieved viral load suppression to less than 50 copies/mL, whereas in the nelfinavir arm, the proportions were 60% and 81%, respectively.

Delavirdine, an NNRTI, inhibits cytochrome P450 3A metabolism and thereby enhances the pharmacokinetic profile of selected protease inhibitor agents, such as indinavir and saquinavir-soft gel capsule. Dual-combination therapy trials exploiting the pharmacokinetic enhancement provided by delavirdine on

several protease inhibitors are in progress.

Conway and colleagues (Abstract 331) reported the 24-week results of an open-label, randomized trial that compared the virologic and immunologic efficacy of 3- and 4-drug combination regimens of zidovudine/lamivudine/saquinavir/delavirdine. Pharmacokinetic profiles of saquinavir alone or in combination with delavirdine were assessed in twice-daily and 3-times-a-day regimens. A total of 94 treatment-naive patients with screening HIV RNA levels higher than 5000 copies/mL (mean baseline HIV RNA: 4.7 to 4.9 $\log_{10}$ copies/mL) were randomized to 4 study groups:

- Group 1 (n = 24): saquinavir (1400 mg bid)/lamivudine (150 mg bid)/delavirdine (600 mg bid)
- Group 2 (n = 24): saquinavir (1000 mg tid)/lamivudine (150 mg bid)/delavirdine (400 mg tid)
- Group 3 (n = 24): saquinavir (1200 mg tid)/lamivudine (150 mg bid)/zidovudine (200 mg tid)
- Group 4 (n = 25): saquinavir (1400 mg bid)/lamivudine (150 mg bid)/delavirdine (600 mg bid)/zidovudine (300 mg bid)

At 24 weeks in an ITT analysis (non-complete = failure), the proportions of patients who achieved HIV RNA levels below 400 copies/mL were as follows: group 1, 83%; group 2, 48%; group 3, 63%; and group 4, 76%. Group 1 (bid dosing) patients achieved greater rates of virologic suppression at week 24 compared to the group 2 (tid dosing) patients (P = .0127). Similarly, virologic response rates were superior in group 4 (bid arm) compared to group 2 (tid arm; P = .0438). When patients experienced viral rebound on delavirdine plus lamivudine-containing regimens (n = 23), the M184V mutation was the first mutation to develop when genotypic resistance was documented. Steady-state pharmacokinetics for saquinavir and delavirdine were conducted at week 4 and supported the use of delavirdine 600 mg plus saquinavir 1400 mg in a twice-daily regimen (Table 4). The 3-times-a-day arm (group 2) demonstrated inferior rates of viral suppression at week 4 compared to the twice-daily regimens in groups 1 and 4, favoring the use of twice-daily regimens. The study drugs were well tolerated; the incidence of clinically significant delavirdine-associated rash was low (<5%). Grade 3 to 4 transaminitis was infrequently observed with delavirdine in this study (<5%).

Investigational Protease Inhibitor Agents. BMS-232632 is an investigational protease inhibitor with potent in vitro antiviral activity (EC_{50}, 2–5 nmol/L), a favorable resistance profile, and pharmacokinetic metabolism that allows for once-daily dosing. Squires and colleagues (Abstract 15) presented the results of a phase 2, 2-stage, randomized trial that compared virologic efficacy and safety of 3 doses of BMS-232632 with nelfinavir (750 mg tid), both as monotherapy (2 weeks) and then in combination with didanosine plus stavudine in treatment-naive subjects. Patients with screening HIV RNA levels higher than 2000 copies/mL were randomized to stage I (n = 98), which evaluated safety and efficacy through week 48, or stage II (n = 322), which has follow-up through week 24. Baseline HIV RNA levels were 4.8 and 4.71 $\log_{10}$ copies/mL in stage I and stage II, respectively. The initial phase of these 2 studies evaluated 3 different BMS-232632 doses: 200, 400, and 500 mg/d; a subsequent comparative phase then evaluated these 3 doses in combination with stavudine/didanosine versus nelfinavir in combination with stavudine/didanosine. The stage I group had durable viral load responses at week 48, as shown by a median reduction of HIV RNA levels of 2.3 to 2.8 $\log_{10}$ copies/mL. In the stage II study, the BMS-232632 arms achieved a median reduction in HIV RNA levels of 2.5 to 2.6 $\log_{10}$ copies/mL at week 24. In an ITT analysis, 65% to 68% of patients in the BMS-232632 arms achieved viral suppression to below 400 copies/mL at week 24 compared to 63% of patients in the nelfinavir arm. At week 24, 30% to 35% (ITT) of patients in the 2 higher-dose BMS-232632 arms (400 and 500 mg/d) achieved HIV RNA levels below 50 copies/mL. The BMS-232632 arms in stage II sustained a median rise in CD4+ cell count of 100/µL at week 24.

The most common adverse event in the BMS-232632 group was diarrhea (20%) versus 50% in the nelfinavir group. The most frequent laboratory abnormality observed in the BMS-232632 group was an asymptomatic dose-dependent elevation in grade 3 or 4 unconjugated bilrubin levels: 74% across 3 BMS-232632 treatment arms; 42% (n = 31) in the 500 mg/d arm. Grade 3 or 4 AST/ALT elevations in stage II were seen in 3 (3%) and 5 (6%) of patients in the 200 mg/d dosing group, 8 (10%) and 10 (12%) in the 400 mg/d dose group, and 4 (6%) and 4 (6%) in the 500 mg/d arm versus 3 (4%) in the nelfinavir arm. All BMS-232632 arms demonstrated an early rise in cholesterol levels; the high-density lipoprotein fraction increased in all 3 arms and there was no change in low-density lipoprotein levels seen in the arms. Based on these study results, the 400 mg/d BMS-232632 dose has been selected for phase 3 studies. The elevations in bilirubin levels were readily managed, and a dose reduction in BMS-232632 was required in less than 3% of patients.

GW433908, the calcium phosphate ester prodrug of amprenavir, is more water soluble than amprenavir, which eliminates the need for a complex formulation and thereby reduces the size and daily pill count required to deliver an equivalent plasma exposure of amprenavir.

Wood and colleagues (Abstract 333) presented the results of a randomized, double-blind, crossover study in which HIV-infected, treatment-naive patients were randomized to GW433908 1395 mg (3 tablets) or 1860 mg (4 tablets) twice daily, or to amprenavir 1200 mg for 28 days. After day 28, amprenavir subjects crossed over to one of the GW433908 doses, and both GW433908 groups crossed over to amprenavir until day 42. All dosing groups received abacavir plus lamivudine twice daily. Both GW433908 dosing regimens (1395 mg bid and 1860 mg bid) delivered equivalent plasma amprenavir exposure ($AUC_{\square ss,}$) as compared to amprenavir 1200 mg twice daily. The GW433908–containing arms had a median 2 $\log_{10}$ copies/mL decrease in plasma HIV RNA levels over 28 days of treatment (median □1.97 and □1.88 $\log_{10}$ copies/mL change in viral load in the 1395 mg and 1860 mg GW433908 dosing arms, respectively, compared with □1.98 $\log_{10}$ copies/mL in the amprenavir arm). Median increases in CD4+ count at week 4 were similar in the 3 treatment arms: 111 and 106 cells/µL, respectively, in the 2 GW433908 dosing arms compared to 92 cells/µL in the amprenavir arm. Both GW433908 doses were well tolerated. The GW433908-treated patients experienced more headache (5%) and sleep disorders (7%) compared to the amprenavir group.

Streamlined Dosing Regimens

Indinavir vs Indinavir/Ritonavir. The week-24 results of the NICE Study (Abstract 334) were presented by Harley and colleagues. This multicenter, randomized, open-label trial evaluated the adherence and convenience in HIV-infected subjects currently taking indinavir every 8 hours and maintaining viral suppression who were randomized to receive an indinavir 400

mg/ritonavir 400 mg twice-daily regimen or to continue indinavir 800 mg every 8 hours plus 2 nRTIs. Randomization to the indinavir/ritonavir and indinavir arms was conducted at 4:1; 345 and 84 patients with baseline mean CD4+ cell counts of 571/µL and 544/µL, respectively, were randomized to the indinavir/ritonavir and indinavir arms. Patients in the indinavir/ritonavir arm underwent a dose escalation over several days to achieve the final indinavir 400 mg/ritonavir 400 mg twice-daily dose. While a higher proportion of patients randomized to the indinavir/ritonavir arm compared to the indinavir arm maintained HIV RNA levels less than 400 copies/mL at 24 weeks (92% vs 88%), the difference in response rates was not significant.

The indinavir/ritonavir arm had a higher rate of premature study treatment discontinuations (22%) due to adverse events than the indinavir arm (12%). Overall adherence was similar between the indinavir/ritonavir and indinavir arms; 30% of patients in the indinavir arm continued to miss the midday dose over the 24-week period. A higher proportion of patients in the indinavir/ritonavir arm developed elevated fasting triglyceride levels (27/228; 12%) compared to the indinavir arm (2/61; 3%; P = .054). One case of nephrolithiasis was observed in the indinavir arm during study follow-up. Switching from indinavir every 8 hours to the indinavir 400 mg/ritonavir 400 mg twice daily regimen in this patient cohort was not associated with any increased rates of viral rebound and was well tolerated in patients who remained on indinavir/ritonavir through week 24.

Once-Daily Dual Protease Inhibitor Therapy. Selected ritonavir-containing dual-based protease inhibitor therapy exhibits potent anti-HIV activity and allows for once-daily dosing regimens with improved adherence.

Suleiman and colleagues (Abstract 336) presented the week-24 results of the phase 2, open-label 48-week Merck 103/104 trial that evaluated the virologic efficacy of indinavir/ritonavir (1200 mg/200 mg) once-daily in combination with stavudine plus lamivudine twice daily in treatment–naive patients with screening plasma HIV RNA levels of 5000 copies/mL or higher and CD4+ cell counts of 50/µL or higher. Forty patients with median baseline viral load of 4.91 $\log_{10}$ copies/mL and CD4 count of 329/µL were enrolled. In an ITT analysis (noncompletion = failure [NC=F]) conducted at 24 weeks, the proportions of patients who achieved viral suppression less than 400 copies/mL and less than 50 copies/mL were 71.8% and 53.8%, respectively. There have been 8 study discontinuations through week 24; 5 of these patients were lost to follow-up. The indinavir/ritonavir once-daily dual protease inhibitor regimen was well tolerated. Adverse events of grade 2 or 3 were reported in 16 (40%) of 40 patients; 1 case of nephrolithiasis with renal colic was reported. Modest increases in lipids were observed at week 24 (median changes in fasting triglyceride and cholesterol levels were 14 mg/dL and 35 mg/dL, respectively).

When low-dose ritonavir is added as an inhibitor of amprenavir metabolism, amprenavir plasma trough concentrations (C_{min}) increase approximately 5-fold above concentrations seen with amprenavir alone. These increased C_{min} values provide greater drug exposure for both sensitive and resistant HIV-1 viral isolates and result in increased protein-adjusted C_{min}/IC_{50} ratios.

The preliminary efficacy and safety week-12 results of the APV20001 study, which compared an amprenavir 1200 mg/ritonavir 200 mg once-daily regimen to an amprenavir 600 mg/ritonavir 100 mg twice-daily regimen in combination with abacavir plus lamivudine in 78 HIV-infected subjects, were presented by Wood and colleagues (Abstract 332). The study design of this trial featured a randomized 6-week pharmacokinetic phase, followed by an open-label phase in which subjects were allowed to select 1 of 3 treatment options: amprenavir 1200 mg twice daily, amprenavir 600 mg/ritonavir 100 mg twice daily, or amprenavir 1200 mg/ritonavir 200 mg; background nRTI therapy (lamivudine/abacavir) was used in all 3 study drug options. At the time of the switch, 89% of subjects had HIV RNA levels below 400 copies/mL. This analysis compared the amprenavir/ritonavir twice-daily arm (n = 21) to the amprenavir/ritonavir once-daily arm (n = 15). Median baseline viral loads and CD4+ cell counts were 4.80 $\log_{10}$ copies/mL and 348/µL, respectively, in the amprenavir/ ritonavir bid arm; 4.85 $\log_{10}$ copies/mL and 182/µL, respectively, in the amprenavir/ ritonavir once-daily arm. At 12 weeks of the open-label phase, 72% of the patients in the amprenavir/ritonavir twice-daily arm had maintained HIV RNA levels below 400 copies/mL compared to 100% of patients in the amprenavir/ritonavir once-daily arm. Median CD4+ cell responses continued to increase over 20 weeks in both arms (+215/µL and +161/µL in the amprenavir/ritonavir bid and amprenavir/ritonavir once-daily arms, respectively). Pharmacokinetic interactions of amprenavir/ritonavir dosing regimens in this trial are detailed in Table 4. The study drug regimens were well tolerated; mild-moderate nausea, vomiting, and diarrhea were the most frequently reported (5%–7%) clinical side effects. Grade 2 fasting cholesterol levels were observed in 25% and 13% of the patients in the amprenavir/ritonavir twice-daily and amprenavir/ritonavir once-daily arms, respectively. Grade 2 fasting triglyceride levels were seen only in the amprenavir/ritonavir twice-daily arm (10%); only 1 patient in this arm experienced grade 3 elevated fasting triglyceride levels.

Once-Daily Lamivudine. The 24-week results of the COLA4005 study, a prospective, randomized, open-label trial that compared the virologic efficacy and safety of switching to once-daily lamivudine (300 mg) with continued standard dosing of lamivudine (150 mg bid) in combination with stable background protease inhibitor–based therapy, were presented by Sension and colleagues (Abstract 317). Subjects with a stable prestudy regimen of lamivudine/stavudine plus either indinavir or nelfinavir for longer than 6 months with HIV RNA levels below 400 copies/mL for at least 3 months were eligible. The baseline median viral load and CD4+ cell count were 49 copies/mL and 514/µL, respectively, in the lamivudine once-daily arm, and 49 copies/mL and 532/µL, respectively, in the lamivudine twice-daily arm. In the ITT (exposed) analysis (M = F), the proportions of patients who maintained HIV RNA levels below 400 copies/mL at week 24 were 95% (35/37) in the once-daily arm compared to 90% (38/42) in the twice-daily arm (P = .679). Both lamivudine-containing regimens were safe and well tolerated. The incidence of drug-related adverse events was low (<5%) in each treatment group. This study supports flexible dosing of lamivudine with retained potency in the once-daily dose.

Once-Daily Antiretroviral Combination Regimens. Molina and colleagues (Abstract 321) presented the 64-week results from the ANRS 091 study, an open-label, single-arm multicenter trial that evaluated the virologic efficacy and safety of emtricitabine, an investigational nRTI, didanosine, and efavirenz as a once-daily antiretroviral combination regimen in

treatment-naive patients. The study enrolled 40 patients with median baseline viral load and CD4+ cell count of 4.77 $\log_{10}$ copies/mL and 373/µL, respectively, who received emtricitabine 200 mg once daily, didanosine 400 mg once daily (250 mg/day for patients weighing <60 kg), plus efavirenz 600 mg once daily. In an ITT analysis conducted at week 64, 90% of patients achieved HIV RNA levels less than 400 copies/mL. In a subset of patients with baseline HIV RNA less than 100,000 copies/mL, 88% (7/8) of patients achieved viral load suppression less than 400 copies/mL. Median CD4+ cell counts increased 219/µL above baseline at week 64. From week 24 to 64, 7 (18%) of 40 patients developed new-onset adverse events grade 3 or 4, but only 3 patients discontinued study treatment due to adverse events. No patients developed grade 2 or higher rash in this study interval from week 24 to 64. This once-daily antiretroviral regimen conferred long-term durable viral suppression and substantial increases in CD4+ cell responses.

Maggiolo and colleagues (Abstract 320) presented the results of a prospective, single-arm, open-label study that evaluated the virologic efficacy and safety of a once-daily regimen featuring didanosine (300 mg qd), lamivudine (300 mg qd), and efavirenz (600 mg qd) in 75 HIV-infected, treatment–naive patients. A total of 41.3% of the patients were coinfected with hepatitis C. Median baseline viral load and CD4+ cell count were 123,000 copies/mL and 251/µL, respectively. At week 48, 77% (ITT) and 93.6% (as-treated analysis) of patients achieved HIV RNA levels below 50 copies/mL. In an ITT analysis, 76.3% of patients with baseline HIV RNA greater than 100,000 copies/mL had viral load suppression below 50 copies/mL at week 48 compared to 78.3% of patients with baseline HIV RNA below 100,000 copies/mL. In a subset of patients with baseline CD4+ cell count below 200/µL, 65.5% of patients achieved suppression below 50 copies/mL at week 48 (ITT) compared to 87.5% of patients with baseline CD4+ cell count above 200/µL. A median CD4+ cell count increase from 250/µL at baseline to 449/µL at week 48 was observed. Study discontinuations occurred in 15 (20%) of 75 patients (virologic failure in 4 patients, 7 patients due to adverse events, 3 patients were nonadherent, and 1 death not attributed to study drugs). Virologic failure (defined as confirmed HIV RNA level >500 copies/mL) was documented in 4 patients: 4 patients developed the M184V mutation and 1 patient had the K103N mutation on genotypic profile. This once-daily antiretroviral regimen provided a median reduction of 3.4 $\log_{10}$ copies/mL in viral load.

Treatment of Primary Infection

Hecht and colleagues (Abstract 407) presented the results of a randomized trial that evaluated the virologic and immunologic responses of administering interleukin 2 (IL-2) in combination with antiretroviral therapy in primary HIV infection. Antiretroviral therapy had to be initiated within 12 months of HIV seroconversion, and all patients received zidovudine/lamivudine plus nelfinavir as the initial antiretroviral regimen. Twenty-four patients with more than 24 weeks of antiretroviral treatment were randomized (without blinding) to receive early (E) IL-2 (within 4 weeks of HIV RNA <500 copies/mL) or deferred (D) IL-2 (48 weeks after HIV RNA <500 copies/mL). IL-2 7.5 million U was given subcutaneously twice daily for 5 days every 8 weeks for 6 cycles. Mean baseline CD4+ cell counts were higher in the E versus D IL-2 arms (605/µL vs 428/µL; P = .02) and mean baseline HIV RNA was lower in the E versus D IL-2 arms (4.7 $\log_{10}$ copies/mL vs 5.3 $\log_{10}$ copies/mL; P = .2, *t* test). At week 24 of antiretroviral therapy, the mean increase from baseline in CD4+ cell count was 659/µL in the E IL-2 arm compared with 186/µL in the D IL-2 arm (P = .003). Both memory and naive CD4+ cells increased with IL-2 therapy. Early IL-2 was associated with maintenance of initial CD8+ noncytotoxic cell suppression of HIV replication. The proportions of patients who achieved HIV RNA levels below 50 copies/mL at week 24 were 10/11 (91%) and 7/13 (54%) in the E and D IL-2 arms, respectively (P = .08, Fisher's exact test). Titers of replication-competent HIV did not decrease during IL-2 therapy. Patients with primary infection achieve higher CD4+ cell counts when IL-2 is provided as adjunctive therapy to antiretroviral therapy.

The results of a randomized, controlled pilot study of HAART versus HAART plus IL-2 in patients with recently acquired HIV-1 infection were presented by Dybul and colleagues (Abstract 406). Patients with documented HIV infection occurring less than 6 months previously and CD4+ cell counts above 300/µL were randomized to 4-drug HAART alone or HAART plus subcutaneous IL-2 administered as 3 cycles of 7.5 million IU for 5 days every 8 weeks for 6 months (initiated after achieving HIV RNA <50 copies/mL). Five patients with baseline HIV RNA levels of 5650 to 500,000 copies/mL and mean CD4+ cell count of 528/µL received HAART alone. Four patients with baseline HIV RNA levels of 52,000 to above 750,000 copies/mL and mean CD4+ cell count of 580/µL received HAART plus 3 cycles of IL-2. The HAART–treated patients sustained a mean increase of 48% (549/µL at entry to 791/µL) in CD4+ cell counts at 12 months compared to a 277% increase in CD4+ cell count (574/µL at enrollment to 2042/µL) in the HAART plus IL-2 arm. By regression analysis, HAART plus IL-2 significantly increased CD4+ T cell counts (P = .04) and increased naive CD4+ T cell counts (P = .07). There was no clear effect of 3 cycles of IL-2 on replication–competent HIV in resting CD4+ cells or on HIV-specific immune responses in the patients evaluated over a 12 month follow-up. IL-2 may be useful as adjunctive therapy with HAART for treatment of recent HIV infection to significantly increase absolute and naive CD4+ T cell counts. More prolonged use of IL-2 with HAART may be effective and warrants further evaluation.

The results of a study evaluating the safety and virologic responses of a switch to a ritonavir-boosted amprenavir regimen from an amprenavir-based therapy in patients with recently acquired HIV infection were presented by Markowitz and colleagues (Abstract 405). Thirty-nine patients with median baseline HIV RNA level and CD4+ cell count of 5.31 $\log_{10}$ copies/mL and 503/µL, respectively, were treated within 33 days on average (range, 5–113 days) from onset of symptoms with an amprenavir-based HAART regimen that included abacavir/lamivudine plus indinavir for the first 16 weeks. Twenty-five of 39 patients switched to amprenavir 600 mg/ritonavir 100 mg twice daily after a median of 48 weeks on study. Prior to switch, 4 patients had virologic failure, 4 patients discontinued antiretroviral therapy due to adverse events, and 4 were lost to follow-up. Thirty-three (84.6%) of 39 patients achieved HIV RNA level below detection (<500 copies/mL) within 112 days (range, 5–279 days) after commencing HAART.

After switch to amprenavir/ritonavir, 14 subjects reported improvement in ongoing adverse events, 10 subjects reported no change, and 1 subject had transient worsening. No grade 3 or 4 laboratory adverse

events or significant changes in serum glucose, cholesterol, or ALT/AST have been observed post-switch. To assess antiviral activity, the number of "blips" were determined once individuals reached plasma HIV RNA levels below 50 copies/mL. Of 218 observations in 25 subjects seen monthly pre-switch, there were 20 episodes (9.2%) of isolated detectable HIV RNA measurements. Post-switch, of 94 observations in 25 subjects, there were 8 blips (8.5%). Preliminary pharmacokinetic determinations of the median amprenavir trough level exposure post-switch in 12 subjects was 1.62 µg/mL (range, 0.49–2.68), which was 5-fold higher than amprenavir levels at trough for the amprenavir 1200 mg dose. In a cohort of previously antiretroviral therapy-naive, recently HIV-infected patients, amprenavir 600 mg/ritonavir 100 mg twice-daily antiretroviral therapy regimen provided comparable antiviral activity, afforded an improved adverse event profile, and exhibited a superior pharmacokinetic profile to that achieved with the amprenavir 1200 mg twice-daily dose.

Treatment Responses in Primary HIV Infection

A study that evaluated whether the timing of initiation of HAART in patients with early HIV infection impacts on risk of virologic failure was presented by Geise and colleagues (Abstract 400). Patients in this cohort had early HIV infection and initiated HAART (defined as 3 drugs from at least 2 classes) and subsequently experienced virologic failure (HIV RNA greater than lowest level of detection on 2 consecutive occasions or treatment discontinuation attributed to virologic failure). A Cox proportional hazards analysis was performed that evaluated the effects of delaying HAART on virologic failure. Seventy-nine patients received HAART and 11 (14%) developed virologic failure. Thirty-seven patients started HAART within 120 days (0 failures), 50 within 1 year (1 failure), and 57 within 2 years (4 failures) of seroconversion. Eight (44%) of 18 patients who had received pretreatment prior to HAART developed virologic failure. Patients who delayed HAART for more than 1 year of seroconversion had an odds ratio of 19.34 (P = .005) of subsequent virologic failure compared to those who began therapy within 1 year. When prior antiretroviral therapy was controlled for, the odds ratio for experiencing virologic failure due to delay in HAART therapy for more than 1 year was 9.73 (P = .063) and due to prior antiretroviral therapy was 2.90 (P = .179). Age, baseline CD4+ cell count, baseline HIV RNA level, and adherence had no impact on virologic failure. In this study, delay in initiating HAART for more than 1 year post-seroconversion was associated with greater risk of virologic failure.

The impact on virologic response of pretreatment with mono- or dual-nRTI therapy prior to starting HAART was evaluated in patients not treated with HAART during acute HIV infection (Geise et al, Abstract 401). A group of 15 patients who had received 1 or 2 nRTIs early after primary infection (from 1993 to 1997) subsequently received a HAART (3 drugs from at least 2 classes) regimen and were compared to 14 treatment-naive patients who delayed HAART initiation until after primary infection (120 days within seroconversion). Both groups were evaluated after completing 2 years of HAART. The pretreated group had received exclusive nRTI therapy for a median of 387 days prior to initiating HAART (median of 1015 days post-seroconversion). The treatment-naive group had delayed initiating HAART a median of 434 days (P = .02). At the time of starting HAART both the pretreated and treatment-naive groups had similar median CD4+ cell counts (409 vs 386/µL; P = .98); median HIV RNA levels were 2309 copies/mL in the pretreatment group and 47,661 copies/mL in the treatment-naive group (P = .001). After 2 years of HAART, the pretreated group had a median CD4+ cell count of 687/µL and viral load of 45 copies/mL compared to 642/µL and 45 copies/mL, respectively, in the treatment-naive group (CD4+: P = .83; HIV RNA: P = .5).

Immune Based Therapy

Markowitz and colleagues (Abstract 343) presented the results of the CPCRA 059 study, a multicenter, open-label, randomized trial that evaluated the predictors of CD4+ cell count response with IL-2 adjunctive therapy in HIV-infected patients with CD4+ cell counts higher than 350/µL who were receiving antiretroviral therapy (median duration of prior antiretroviral therapy, 42.2 months). Two hundred fifty-six patients were randomized to receive subcutaneous IL-2 at either 7.5 (n = 126) or 4.5 (n = 130) MIU twice daily. IL-2 was administered for 5 consecutive days every 8 weeks for at least 3 cycles. A total of 192 patients completed 3 or more IL-2 cycles, and 245 patients had CD4+ cell counts at month 12. For regression coefficients (β), CD4+ and body mass index (BMI) were modeled as continuous variables. At baseline, 60% of patients had HIV RNA levels below 50 copies/mL. Median preenrollment nadir and baseline CD4+ cell counts were 293/µL and 538/µL, respectively. Nadir CD4+ cell count was the strongest predictor of CD4+ change from baseline to month 12 (β = .34; P < .0001). Among those who completed more than 3 cycles of IL-2, nadir CD4+ cell count (β = .81; P < .0001) and BMI (β = –21.5; P < .004) were the strongest predictors of CD4+ cell count change from baseline to day 29 after the third IL-2 cycle. Baseline CD4+ cell count was not predictive of CD4+ cell count change after IL-2 therapy (β = .09; P < .62). Nadir CD4+ cell count was highly predictive of CD4+ cell count response following IL-2 therapy, which suggests that immune defects persist despite normalization of CD4+ cell count conferred by antiretroviral therapy.

The ANRS 079 study, an open-label, randomized trial presented by Levy and colleagues (Abstract 344), compared the virologic efficacy and immune responses of subcutaneous IL-2 in combination with HAART to HAART alone in treatment–naive (or protease inhibitor–naive) HIV-infected patients. One hundred eighteen patients with a median baseline CD4+ cell count of 337/µL were randomized to stavudine/lamivudine/indinavir or stavudine/lamivudine/indinavir plus subcutaneous IL-2 therapy (5 MIU bid times 5 days, every 4 weeks for 3 cycles and every 8 weeks for the following 7 cycles). ITT analysis was used. The median increase in CD4+ cell count from baseline was 865/µL in the HAART plus IL-2 arm compared to 240/µL in the control arm (P < .0001). At week 74, 89% of patients in the HAART plus IL-2 arm had sustained an 89% increase in CD4+ cell count from baseline compared to a 44% CD4+ cell count increase in the control arm (P < .0001). At week 74, the proportions of patients with HIV RNA level below 50 copies/mL were 86% to 90% in both arms (P = .7). Mean (SD) plasma HIV RNA $\log_{10}$ copies/mL decreased from 3.86 (1.05) in the HAART plus IL-2 arm to 1.87 (0.57), and 4.04 (0.91) in the control arm to 1.87 (0.57). The mean proviral HIV DNA level in peripheral blood mononuclear cells was 2.58 $\log_{10}$ copies/mL in the HAART plus IL-2 arm and 2.43 $\log_{10}$ copies/mL in the control arm (P = .3). Toxicity associated with IL-2 therapy

resulted in mean dose reductions administered per cycle from 48.5 at cycle 1 to 43 at cycle 10. In this group of treatment-naive patients, IL-2 adjunctive therapy in combination with HAART was generally well tolerated and afforded a greater rise in CD4+ cell counts compared to HAART alone.

Trials in Antiretroviral–Experienced Subjects

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

Viral Rebound in nRTI–Experienced Subjects

The results of the 48-week, randomized, open-label HIV-NAT 005 trial, which compared the virologic efficacy and tolerability of indinavir 800 mg/ritonavir 100 mg twice-daily to indinavir 800 mg 3 times a day in HIV-infected, nRTI-experienced Thai patients, were presented by Boyd and colleagues (Abstract 335). Zidovudine/lamivudine was provided as nRTI therapy to all randomized patients. All eligible patients (n = 104) had prior zidovudine experience in combination with either didanosine or zalcitabine; 39% of patients had received zidovudine monotherapy. The median duration of nRTI therapy prior to study entry was 29 months. The median baseline viral load and CD4+ cell count in the indinavir/ritonavir arm (n = 50) were 4.0 $\log_{10}$ copies/mL and 191/µL, respectively; 4.2 $\log_{10}$ copies/ mL and 143/µL, respectively, in the indinavir arm (n = 54).

In an ITT analysis (M = F), the proportion of patients who achieved HIV RNA levels below 50 copies/mL at week 48 in the indinavir/ritonavir and indinavir arms were 66% and 70%, respectively (P = .6). No significant differences were observed in the median reduction of HIV RNA at week 48 between the 2 arms: 1.6 $\log_{10}$ copies/mL and 2.0 $\log_{10}$ copies/mL in the indinavir/ritonavir and indinavir arms, respectively (P = .7). Similar median rises in CD4+ cell counts were observed in both study arms (70/µL and 57/µL in the indinavir/ritonavir and indinavir arms, respectively) at week 48 (P = .6). Nausea was more frequently reported as an adverse event in the indinavir/ritonavir arm vs the indinavir arm (P = .04). Grade 3 or 4 hyperbilirubinemia (unconjugated) was reported in 34% and 20% of patients in the indinavir/ritonavir and indinavir arms, respectively, but did not require permanent treatment discontinuation. Nephrolithiasis occurred in 20 patients (22% in the indinavir/ritonavir arm and 17% in the indinavir arm; P = .08).

Viral Rebound in NNRTI-Containing Regimens

Capravirine is an investigational NNRTI that has demonstrated potent in vitro antiviral activity against HIV variants with reverse transcriptase mutations, including K103N, which confers broad cross resistance to currently approved NNRTI agents. Wolfe and colleagues (Abstract 323) presented the 12-week preliminary results of a double-blind, placebo-controlled trial which evaluated the antiviral activity and safety of capravirine versus placebo in HIV-infected, protease inhibitor–naive patients experiencing viral rebound (HIV RNA >2000 copies/mL) on an NNRTI-containing regimen. Patients whose baseline median plasma viral load and CD4+ cell count were 4.14 $\log_{10}$ copies/mL and 362/µL, respectively, were randomized to capravirine (1400 mg or 2100 mg bid) or placebo, in combination with nelfinavir plus 2 new nRTIs. Preliminary results of 50 patients with data available showed that 50% of patients randomized to capravirine achieved HIV RNA levels below 400 copies/mL. The higher capravirine dose (2100 mg bid) group experienced more frequent gastrointestinal adverse events of moderate severity: diarrhea, nausea, and vomiting. At week 12, 4 patients had experienced virologic failure and 7 patients had discontinued study treatment because of adverse events. Based on these preliminary results, capravirine demonstrated antiviral activity in patients who had experienced virologic failure on a prior NNRTI-containing regimen. The capravirine 1400 mg bid dose was better tolerated.

Viral Rebound in Protease Inhibitor–Containing Regimens

Gulick and colleagues (Abstract 338) presented the week-48 results of the ACTG 359 trial, which evaluated the virologic efficacy and durability of 2 dual–protease inhibitor salvage therapy regimens, saquinavir soft gel capsule with ritonavir or nelfinavir, plus delavirdine, adefovir dipivoxil, or both in HIV-infected patients with virologic failure (HIV RNA >2000 copies/mL) on an indinavir-containing regimen. The dual–protease inhibitor therapy was provided in open-label fashion; delavirdine, adefovir dipivoxil, and delavirdine plus adefovir dipivoxil were blinded. A total of 277 subjects with median 14-month prior indinavir exposure, baseline HIV RNA level of 31,746 copies/mL, and CD4+ cell count of 229/µL completed 16 weeks of study treatment. At the week-16 primary endpoint, 30% of patients (77/254) achieved HIV RNA levels of 500 copies/mL. Patients with virologic response were eligible for a study extension at week 24; 84 of the 105 eligible patients completed 48 weeks of follow-up. Of the 105 eligible extension subjects, 70 had HIV RNA levels below 500 copies/mL at week 16 and 61% (43/70) had sustained viral load suppression (≤500 copies/mL) at week 48. The median change from baseline CD4+ cell count at week 48 was 72/µL (range, 192 to 808/µL). Patients who maintained HIV RNA suppression sustained significantly higher CD4+ cell count increases at week 48 (P = .033): 102/µL in subjects with HIV RNA of 500 copies/mL or lower (n = 49) versus 20/µL in subjects with HIV RNA above 500 copies/mL (n = 35).

T-20, an investigational fusion inhibitor that targets HIV gp41, was evaluated in a randomized, multicenter, open-label trial in 71 HIV-infected, NNRTI-naive, protease inhibitor-experienced patients. Lalezari and colleagues (Abstract LB5) presented the week-16 analysis of this study, which evaluated the safety of T-20 at 3 different doses (50, 75, and 100 mg bid) administered subcutaneously in combination with abacavir/efavirenz plus amprenavir 1200 mg/ritonavir 200 mg twice daily. A control arm (n = 19) received only abacavir/efavirenz plus amprenavir 1200 mg/ritonavir 200 mg twice daily. Of the 71 randomized patients with median baseline viral load of 19,000 copies/mL and CD4+ cell count of 350/µL, 53 patients completed week 16. Eighteen patients discontinued study participation; 10 discontinued due to adverse events, which were predominantly local injection site reactions, and 8 patients discontinued with systemic reactions, consisting of fever and rash. Two patients in the control arm experienced virologic failure and 2 patients in the T-20 100 mg twice daily arm dose reduced T-20 to 50 mg twice daily. The most frequent adverse event was local injection site reactions: grade 1 injection site reactions occurred in 12 (63%), 12 (57%), and 13 (77%) of the T-20 arms dosed at 50 mg, 75 mg, and 100 mg, respectively. Grade 3 injection site reactions developed in 1, 3, and 1 patients, respectively, randomized to the 50 mg, 75 mg, and 100 mg T-20 arms; only 1 grade 4 local injection site reaction (100 mg bid T-20 arm) was reported. The most frequent clinical adverse events

Table **2.** Trials in Antiretroviral-Experienced Subjects

Study Name (Abstract No.)	Regimen(s)	No. of Patients	Weeks of Follow-up	Baseline HIV-1 RNA (copies/mL)
HIV-NAT 005: nRTI-Experienced Patients (335)	1. Indinavir 800 mg/ritonavir 100 mg bid plus fixed-dose lamivudine/zidovudine	50	48	4.0 $\log_{10}$ (median)
	2. Indinavir 800 mg tid plus fixed-dose lamivudine/zidovudine	54		4.2 $\log_{10}$
Capravirine in NNRTI-Experienced Patients (323)	1. Capravirine (1400 mg or 2100 mg) bid/2 nRTIs/ nelfinavir	50 (total)	24	4.14 $\log_{10}$ (overall median)
	2. Capravirine placebo bid/2 nRTIs/nelfinavir			
ACTG 359: Indinavir-Experienced Patients (338)	1. Saquinavir soft gel capsule (sgc)/ritonavir bid: saquinavir sgc/ritonavir plus delavirdine, adefovir, or delavirdine/adefovir	105 (total)	48	31,746 (overall median)
	2. Saquinavir sgc/nelfinavir bid: saquinavir/nelfinavir plus delavirdine, adefovir, or delavirdine/adefovir			
T-20 in PI-Experienced, NNTRI-Naive Patients (LB5)	1. T-20 (50, 75, or 100 mg bid) plus abacavir/efavirenz/amprenavir plus ritonavir bid	52	16	19,000 (overall median)
	2. Abacavir/efavirenz/amprenavir plus ritonavir bid (control arm)	19		
Intensification of Therapy in Indinavir-Exposed Patients (337)	Indinavir 400 mg/ritonavir 400 mg bid plus 2 nRTIs (switched from indinavir 800 mg tid + 2 nRTIs)	37	48	3.3 $\log_{10}$ (median)
DMP-049: PI-Experienced Patients (20)	1. PI plus nRTIs (continued PI therapy)	105	48	<50
	2. Efavirenz 600 mg/d plus nRTIs (substitution of PI with efavirenz)	217		<50

nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI indicates protease inhibitor; ITT indicates intent-to-treat; M = F indicates missing data equals failure; CNS indicates central nervous system.

Baseline CD4+ Count (cells/μL)	Plasma HIV-1 RNA Effect	CD4+ Count Change (cells/μL)	Comments
191	66% <50 (ITT analysis; M = F)	+70 (median)	Nephrolithiasis occurred in 22% and 17% of patients in indinavir/ritonavir and indinavir arms, respectively (P = .08). Grade 3 or 4 hyperbilirubinemia was reported in indinavir/ritonavir (34%) and indinavir (20%) arms.
143	70% <50	+57	
362 (overall median)	50% <400 (at week 12)	N/A	Capravirine 1400 mg bid dose was better tolerated. At week 12, 4 patients in capravirine arm had virologic failure and 7 had discontinued study treatment owing to adverse events.
229 (overall median)	67% (70/105) ≤500 at week 16 (ITT analysis)	+72 (overall median)	Patients who maintained HIV-1 RNA levels ≤500 copies/mL had higher CD4+ cell count increases at week 48: 102/μL vs 20/μL in group with HIV-1 RNA >500 copies/mL (P = .033).
	61% (43/70) ≤500 at week 48		
350 (overall median)	T-20 arms (grouped): 71% <400, 48% <50 (ITT analysis; M = F)	+37 (50 mg), +74 (75 mg), +74 (100 mg) (median)	Most frequent adverse event reported with T-20 was local injection reactions: 66% of patients had reactions. Most frequent systemic clinical adverse events were nausea, diarrhea, fatigue, and rash; no definite relation to T-20 exposure demonstrated. No differences in grade 3 or 4 laboratory abnormalities among treatment arms noted.
	58% <400, 37% <50	+10	
325	63% <400, 38% <50	+47 (mean)	Patients with 0–3 protease mutations at baseline had greater virologic response rates (HIV-1 RNA change of ≥0.5 $\log_{10}$ copies/mL from baseline) vs those who had 4–7 protease mutations (71% vs 43%). Moderate hyperlipidemia developed in 49% of patients who switched to indinavir/ritonavir therapy.
550 (median)	73% <50 (ITT analysis; M = F) (P = .02)	+64 (mean)	Higher rates of viral rebound (HIV-1 RNA >50 copies/mL) occurred in the PI arm (15%) vs the efavirenz (7.3%) arm (P = .024). CNS symptoms were more frequent in the efavirenz arm (23%) vs the PI arm (2%) (P < .001). Adherence (number of patients who missed several doses) was better in the efavirenz arm vs the PI arm (P < .001).
534	84% <50	+34	

(excluding injection site reactions) were nausea, diarrhea, fatigue, and rash; there was no consistent dose-response adverse event association with T-20 observed. No definite relationship to T-20 exposure and systemic reactions was demonstrated. There were no significant differences in frequency of grade 3 or 4 laboratory abnormalities among the treatment arms. A grade 4 neutropenia was reported in the T-20 50 mg arm.

The study did not assess virologic efficacy. In an ITT analysis (M = F) at week 16, including patients randomized and dosed, 71% and 48% of patients in the T-20 arms (grouped) achieved HIV RNA levels below 400 copies/mL and below 50 copies/mL, respectively, compared to 58% and 37% of patients, respectively, in the control arm. In an ITT analysis of patients randomized, dosed, and remaining on study treatment, 82% and 56% of patients in the T-20 arms (grouped) achieved HIV RNA below 400 copies/mL and below 50 copies/mL, respectively, compared to 58% and 37% of patients, respectively, in the control arm. The highest-dose T-20 arm (100 mg bid) achieved the maximal HIV RNA decline from baseline to week 16: 3.0 $\log_{10}$ copies/mL. There was a median difference between the T-20 100 mg arm and the control arm of 0.6 $\log_{10}$ copies/mL in the reduction of HIV RNA from baseline to week 16. The median rises in CD4+ cell counts from baseline to week 16 were: 37, 74, and 64/µL in the T-20 arms featuring 50 mg, 75 mg, and 100 mg, respectively, compared with 10/µL in the control arm. No dose response was observed in the median CD4+ cell count change at week 16 among the T-20 arms.

Treatment Strategies

Intensification of Antiretroviral Therapy Regimen for Viral Rebound

Hsu et al (Abstract 337) presented the week-48 results of a single-arm, open-label trial which evaluated the virologic efficacy and safety of switching HIV-infected patients experiencing viral rebound on an indinavir-based regimen to an intensified regimen using indinavir/ritonavir (400 mg/400 mg). Eligible patients were currently receiving indinavir 800 mg every 8 hours plus 2 nRTIs for more than 3 months, were ritonavir-naive, and had screening HIV RNA levels between 50 and 50,000 copies/mL. A total of 37 patients with baseline median viral load of 3.3 $\log_{10}$ copies/mL and CD4+ cell counts 325/µL switched to indinavir 400 mg/ritonavir 400 mg twice daily with a dose escalation scheme; stable background antiretroviral therapy was continued. At week 48, the proportions of patients who achieved HIV RNA levels below 400 copies/mL and below 50 copies/mL were 63% and 38%, respectively. A mean increase in CD4+ cell count of 47/µL was sustained at week 48. Pharmacokinetic profiles of the indinavir/ritonavir regimen are described in Table 4. Patients with indinavir C_{min} higher than the median at week 3 sustained a greater reduction in HIV RNA at week 48 compared to those patients whose indinavir C_{min} was lower than the median (HIV RNA <400 copies/mL: 88% vs 29%). Baseline genotype was available for 30 subjects: the number of protease mutations ranged from 0 to 7. There was a greater than 25% prevalence of baseline protease mutations at codons 10, 46, 54, 71, 82, and 90. Patients with 0 to 3 protease mutations at baseline had greater virologic response rate (defined as HIV RNA change of at least 0.5 $\log_{10}$ from baseline) compared to those with 4 to 7 baseline protease mutations (71% vs 43%). Hyperlipidemia of moderate severity developed in 18 (49%) of 37 subjects switched to indinavir/ritonavir-based therapy.

Substitution of NNRTI for Protease Inhibitor in Individuals with Viral Suppression

The results of the 48-week prospective, randomized, open-label DMP 049 trial, which compared the viral load suppression (HIV RNA <50 copies/mL) in patients who continued a protease inhibitor-containing regimen to those on an NNRTI (efavirenz)-based regimen, were presented by Becker and colleagues (Abstract 20). A total of 346 patients with suppression of viral load (<50 copies/mL) on a protease inhibitor-containing regimen and mean duration of protease inhibitor experience of 21 months were randomized 2:1 to substitute protease inhibitor(s) with efavirenz 600 mg/d (n = 217) or to continue the protease inhibitor-containing regimen (n = 105); stable nRTI background therapy was continued. Median CD4+ cell counts were 534/µL and 550/µL in the efavirenz and protease inhibitor arms, respectively. The prior antiretroviral therapy regimens were similar between the efavirenz and protease inhibitor arms: 44% vs 46%, 56% vs 52%, and 34% vs 28% of patients in each arm were receiving indinavir therapy, zidovudine plus lamivudine, or stavudine plus lamivudine, respectively, at study entry. Twelve percent of patients randomized to the protease inhibitor continuation arm were not dosed compared to 4% in the efavirenz arm (P = .006).

At week 48 (ITT), the proportions of patients who had HIV RNA levels below 50 copies/mL were 84% and 73% in the efavirenz and protease inhibitor arms, respectively (P = .02). Virologic failure (defined as confirmed HIV RNA >50 copies/mL) rates at week 48 were 7.3% and 15% in the efavirenz and protease inhibitor arms, respectively (P = .024). A median CD4+ cell count rise of 60/µL was observed. There were no significant differences in mean CD4+ cell count increases at week 48 between the efavirenz and indinavir arms (34 and 64/µL, respectively). No significant differences between baseline and week 48 nonfasting cholesterol levels were noted in the efavirenz and protease inhibitor arms. Adverse events reported in the efavirenz and indinavir arms: central nervous system symptoms (23% vs 2%; P < .001); rash (5% vs 2%; P = NS); and lipodystrophy (0% vs 3%; P = .03). Adherence was significantly better in the efavirenz arm: 29% of patients in the efavirenz arm versus 43% in the indinavir arm missed at least 1 dose (P = .011); multiple doses were more frequently missed in the indinavir arm compared to the efavirenz arm (P < .001). The substitution of a protease inhibitor with efavirenz was well tolerated and associated with continued suppression of viral load, similar CD4+ cell count rises, and an improved antiretroviral therapy adherence profile.

Timing of Initial Antiretroviral Therapy

Several trials presented at the Conference evaluated the impact of delayed vs earlier initiation of antiretroviral therapy on survival, long-term immune responses, and progression to AIDS.

The results of a prospective, case control study conducted within the Swiss HIV Cohort, which evaluated the clinical benefit of initiating antiretroviral therapy in asymptomatic HIV-infected patients with CD4+ cell counts above 350/µL, were presented by Opravil and colleagues (Abstract LB6). A total of 358 treatment-naive patients with CD4+ cell counts above 350/µL started antiretroviral therapy between January 1996 and December 1999 and had at least 1 year of follow-up (treat-

ed group); 358 treatment-naive case controls who did not start treatment were matched by age (±20%), baseline HIV RNA (±0.5 $\log_{10}$ copies/mL), CD4 count (±20%), and sex (untreated controls). Baseline characteristics in the 2 groups (treated vs untreated) were: women (28% vs 33%), transmission routes of HIV acquisition (25% intravenous drug use in both groups). The baseline median viral loads were 4.26 $\log_{10}$ copies/mL and 4.10 $\log_{10}$ copies/mL in the treated and untreated groups, respectively (P = .15); baseline median CD4+ cell counts were 485/µL and 487/µL, respectively (P = .91). The treated group had a median follow-up time of 2.27 years compared to 1.27 years for the untreated group (P < .001). In the treated group, 51 (14.2%) of patients were lost to follow-up compared to 103 (28.8%) patients in the untreated group. The following clinical endpoints were assessed over 4 years of follow-up in the treated versus untreated groups (no. [%]):

- Progression to CDC stage B/C: 16 (4.5%) vs 62 (17.3%); P < .0001
- Progression to CDC stage C: 3 (0.8%) vs 16 (4.5%)
- Progression to death (all causes): 5 (1.4%) vs 19 (5.3%)

In a multivariate analysis, the hazard ratio was 0.15 for CDC stage B/C event and 0.12 for death (P < .001) in the group that started antiretroviral therapy versus those who deferred (untreated). Viral load at baseline was highly predictive for progression to CDC stage B/C: hazard ratio of 2.10 per $\log_{10}$ HIV RNA. The untreated group had a higher drop-out rate and shorter median follow-up. In the treated group (n = 333; 25 patients in strategic treatment interruptions were excluded), 200 (60.1%) changed 1 drug or more. Reasons for stopping at least 1 drug in the treated group included: 15 (4.5%) experienced virologic failure, 97 (29.1%) had intolerance and adverse events, 45 (13.5%) patient's decision, 9% for other causes. Forty-one percent of the treated group underwent at least 1 treatment interruption, and 19.5% were not receiving antiretroviral therapy at the end of follow-up. In this study, the risk of HIV disease progression was lowered by 7- to 8-fold if antiretroviral therapy was initiated in asymptomatic patients with CD4+ cell counts higher than 350/µL. If patients were untreated, the risk of progressing to AIDS was 4.5% and to death was 5.3%.

Hogg and colleagues (Abstract 342) presented the results of a study that evaluated the effectiveness of antiretroviral therapy initiated in HIV-infected, treatment-naive individuals at different CD4+ cell and HIV RNA thresholds. A population-based analysis was conducted in 1219 subjects (909 on protease inhibitor- and 310 on NNRTI-containing regimens) who started antiretroviral therapy between August 1996 and September 1999. Rates of progression from start of treatment to death were stratified using CD4+ cell and HIV RNA thresholds. As of January 2000, 72 AIDS-related deaths had occurred, yielding a crude mortality rate of 5.9%. The cumulative mortality rate at 12 months was 3.2% ± 0.5%. In multivariate analyses, only CD4+ cell count remained significantly associated with death; prior AIDS diagnosis and baseline HIV RNA levels were not significant predictive factors. After adjusting for AIDS diagnosis and baseline HIV RNA levels, the adjusted odds ratio for progression to death was 7.36 (95% CI, 3.82–14.2; P < .001) in patients with CD4+ cell counts below 50/µL and 3.17 (95% CI,1.69–5.93; P < .001) in patients with CD4+ cell counts between 50 and 199/µL, compared to those with CD4+ cell counts above 200/µL. In this study, patients who initiated HAART at CD4+ cell counts below 200/µL had a significantly increased risk of mortality. The effectiveness of antiretroviral therapy was dependent upon CD4+ cell counts but independent of baseline HIV RNA levels, prior AIDS diagnosis, protease inhibitor use, or age.

Sterling and colleagues (Abstract 519) reported the results of a study that evaluated the impact of initiating HAART on HIV disease progression with a combined study endpoint (new AIDS defining event or death). One thousand fourteen HIV-infected patients were enrolled within 90 days of the first viral load into group 1 (HAART) or group 2 (no HAART); the study period extended from July 1, 1996, to June 30, 2000. The HAART group (n = 530) had received antiretroviral combination treatment for at least 90 days (protease inhibitor, NNRTI, or triple nRTI) and the no-HAART group (n = 484) had received only dual-nRTI therapy or no antiretroviral therapy. Baseline characteristics: injection drug use as risk factor for HIV acquisition was reported in 27% of patients in the no-HAART group versus 14% in the HAART group (P < .01); 25% of patients in the no-HAART group had baseline CD4+ cell count above 200/µL versus 54% in the HAART group (P < .01). Baseline HIV RNA level below 20,000 copies/mL: 34% and 51% of patients in the HAART group and no-HAART group, respectively (P < .01); baseline HIV RNA level above 100,000 copies/mL: 37% and 19%, respectively (P < .01). The loss to follow-up was greater in the no-HAART arm (7%) compared to the HAART arm (3%; P < .01). In patients with CD4+ cell count below 200/µL, there was no statistical difference in disease progression between individuals with baseline HIV RNA levels below 20,000, 20,000 to 100,000, and more than 100,000 copies/mL. Similarly, baseline HIV RNA levels in the patients with CD4+ cell counts 201 to 350/µL or more than 350/µL did not predict disease progression. In the group with CD4+ cell counts below 200/µL, there was a significant difference in disease progression between those receiving HAART versus no HAART; the HAART group progressed more slowly (P = .005).

Among patients with baseline CD4+ cell counts 201 to 350/µL, however, no difference in disease progression was observed between the HAART and no-HAART groups. In a Cox proportional hazards model of disease progression among patients receiving HAART, the relative hazard for disease progression in patients with CD4+ cell count below 200/µL was 4.23 (95% CI, 2.38–7.53; P < .001); in patients with CD4+ cell count of 201 to 350/µL, it was 1.60 (95% CI, 0.81–3.15; P = .17), compared to those patients with CD4+ cell counts above 350/µL. In this study, CD4+ cell count was a better predictor of response to HAART than baseline viral load. Since no difference in disease progression was seen in patients with CD4+ cell counts of 201 to 350/µL who received HAART versus no HAART, these results suggest that treatment may be initiated at lower CD4+ cell counts. The limitations of study interpretation include a greater loss to follow-up in the no-HAART group (7%) and the short duration of follow-up (2 years).

Kaplan and colleagues (Abstract 520) reported the results of an observational study which assessed the risk of HIV-related death among HIV-infected patients initiating 2- or 3-drug antiretroviral therapy in 1994 or later. The enrolled patients were participating in the CDC Adult and Adolescent Spectrum of Disease Project, which conducted medical record review surveillance. Risk was assessed as a function of CD4+ cell count at the time of initiation of antiretroviral therapy (lowest count within 12 months prior to starting antiretroviral therapy): 2-year survival was estimated by the method of Kaplan and Meier and the hazard ratio for death was estimated in a Cox proportional model. Adjusting for age, HIV exposure mode, his-

tory of AIDS (opportunistic infections), and 2- versus 3-drug antiretroviral therapy, an ITT analysis was used. A total of 5110 patients were included in the analysis, for a total of 8428 person-years of follow-up (median duration of follow-up was 17 months). Median age was 35 years, 78% were men; 31% were white, 49% African American, 19% Hispanic; 16% were injection drug users and 42% were men who have sex with men. Nine hundred two deaths were included in the analysis.

The majority of deaths occurred in patients with the lowest CD4+ cell counts: 603 deaths occurred in the group with CD4+ cell counts between 0 and 49/μL. Patients with CD4+ cell counts between 0 and 49/μL had an estimated 2-year survival rate of 64.8% (hazard ratio of 5.5) compared to a 96.5% survival rate in patients with CD4+ cell counts 500/μL or higher. Two-year survival was only significantly decreased in patients starting antiretroviral therapy with CD4+ cell counts of less than 150/μL. The hazard ratio was 1.8 in patients with CD4+ cell counts of 200 to 350/μL. Initiating antiretroviral therapy with 2- versus 3-drug combination regimens was associated with a hazard ratio of 1.5, and a history of AIDS-defining opportunistic infections was associated with a hazard ratio of 2.6; both were statistically significant. A total of 2854 (56%) of 5110 patients started 3-drug therapy, and 330 (37%) of 902 deaths occurred in this group.

In this study, the risk of death was significantly higher in patients who initiated antiretroviral therapy at CD4+ cell counts below 200/μL compared to those with higher counts. The risk of death also appears to be higher in the group with CD4+ cell counts between 200 and 349/μL. These results suggest that antiretroviral therapy should be started at a higher CD4+ cell count (>200/μL) and not deferred until it declines to below 200/μL. The optimal CD4+ cell count range to initiate antiretroviral therapy has not yet been defined. There are several important limitations in this study which should be noted: it was an observational study, the status of antiretroviral therapy-naive patients was uncertain, there was a short follow-up period, adherence was not monitored, drug toxicities were not reported, and resistance profiles were not evaluated.

Chen and colleagues (Abstract 341) presented the results of a survival analysis that was conducted using an observational database of a prospectively followed cohort at the University of Alabama. Of 1037 patients who initiated HAART after January 1996, there were CD4+ cell count data within 3 months of starting therapy for 759 patients and follow-up data for 715 patients. Kaplan-Meier analyses were used to assess correlations between independent factors and mortality. Patients were stratified by CD4+ cell count at the time of starting treatment. The median duration of follow-up was 3 years; 99 (13.8%) of patients died. Patients with baseline CD4+ cell counts below 200/μL ($P = .002$) and with a prior history of opportunistic infection ($P < .004$) at the time of initiating HAART had a higher mortality rate. Four-year survival for patients who began HAART with CD4+ cell counts below 200/μL was 65% compared with 85% for those starting with CD4+ cell counts above 200/μL. Age, race, gender, baseline viral load, duration of antiretroviral therapy prior to HAART, use of a protease inhibitor-containing regimen, and number of antiretroviral therapy regimens prior to the start of HAART were not associated with survival. In this study, the patients who deferred initiation of HAART until CD4+ cell counts of less than 200/μL had a significantly higher risk of mortality. Based on these findings, efforts should be targeted to diagnose HIV infection at an earlier stage of disease (CD4+ cell count above 200/μL) to optimize clinical benefit associated with initiation of HAART.

Primary Infection and Transmission of Drug-Resistant Virus

There were several presentations detailing the prevalence of HIV drug resistance in recent HIV seroconverters and in antiretroviral-naive subjects, and these are summarized in Table 3. Yerly and colleagues (Abstract 754) described changes in the frequency of HIV drug resistance among 197 subjects with primary HIV infection in the Swiss HIV Cohort Study between 1996 and 1999. In the population studied the mean viral load and CD4+ cell counts were greater than 5.0 $\log_{10}$ copies/mL and 600/μL, respectively. For the years 1996, 1997, 1998, and 1999, the prevalence of drug resistance was 8.6%, 14.6%, 8.8%, and 5%, respectively. Drug resistance mutations were observed more frequently in men than women, being 10% and 2.6%, respectively. In the specific risk groups with recent HIV seroversion, drug resistance mutations were observed in 11.3%, 6.1%, and 13% of seroconverting homosexual men, heterosexual men, and intravenous drug users, respectively. The mutations observed were zidovudine-associated in 11 (5.8%; most with changes at codon 215), the M184V mutation in 3 (1.6%), NNRTI-associated in 2 (1.6%) and protease inhibitor-associated in 1 (0.6%; any major mutation). The prevalence of non-B subtypes increased over time, from 23% in 1996 to 35% in 1999. Drug resistance mutations were observed in only 1 non-B subtype isolate. Specific patients were described in whom transmission was believed to have occurred prior to the onset of the acute HIV seroversion illness. The authors suggest that the apparent decrease in the frequency of drug resistance may be due to the increasing prevalence of non-B subtypes and to the increasing frequency of suppression of viremia to below 400 copies/mL, being 10% in 1996 and 53% in 1999.

Little and colleagues (Abstract 756) described the prevalence of phenotypic drug resistance among 108 subjects in 9 North American cities over the years 1996 through 2000. Comparing the years 1996 to 1997 with 1999 to 2000, the frequency of isolates with more than 10-fold nRTI, NNRTI, and protease inhibitor resistance rose from 2.7% to 8.2% ($P = .03$), from 1% to 7% ($P = .007$), and from 2% to 8% ($P = .001$), respectively. The frequency of isolates with more than 10-fold resistance to 2 or more drugs rose from 0.4% to 5.3% ($P = .002$). The time to virologic suppression was significantly increased in those with more than 10-fold resistance to 1 or more drugs ($P = .04$). These data highlight potentially increasing rates of HIV drug resistance transmission in North America.

Tasker and colleagues (Abstract 436) determined the prevalence of genotypic and phenotypic antiretroviral drug resistance in a cohort of military recruits (n = 103) with recent HIV seroconversion and observed how this affected blinded treatment outcomes at 6 months. Drug resistance mutations were observed in 21 of 103 (20%) at baseline. There were no significant differences in the CD4+ cell counts and the viral loads at baseline between those with and without mutations; these were 498 and 463/μL and 4.7 $\log_{10}$ and 4.5 $\log_{10}$ copies/mL, respectively. Six-month follow-up data were presented for 80 subjects treated with 3 or more antiretrovirals. The changes in CD4+ cell counts and viral loads in those with resistant/intermediate (n = 17) and susceptible (n = 63) baseline isolates were +269 and +170/μL ($P < .05$)

and –3.2 $\log_{10}$ and –2.7 $\log_{10}$ copies/mL (P = .14), respectively. Similar results were observed for the 8 subjects with primary resistance mutations at 6 months. This study describes significantly greater on-treatment increases in CD4+ cell counts in the setting of baseline phenotypic or genotypic resistance compared to those with fully susceptible virus.

García-Lerma and colleagues (Abstract 426) evaluated the significance of reverse transcriptase codon changes 215D, C, S, or E observed in a cohort of 437 antiretroviral-naive individuals recently diagnosed with HIV infection. The prevalence of mutations 215D, C, S, and E was 4 (0.9%), 3 (0.7%), 4 (0.9%), and 1 (0.2%), respectively. None of these isolates demonstrated phenotypic zidovudine resistance even in the presence of the M41L or L210W mutations. Notably, the T215D/C-bearing isolates were also associated with the M41L or L210W mutations, suggesting that these may represent revertants from T215Y. Parallel replication capacity assays in the absence of zidovudine favored the 215S mutant over wild-type virus and favored both of these over 215C/D-bearing isolates. These data suggest that in the absence of zidovudine, isolates with these mutations at codon 215 may be stable revertants from the T215Y mutation.

Hecht and colleagues (Abstract 87) evaluated the transmission of drug-resistant HIV in 11 partner pairs believed to have experienced partner-to-partner transmission within 6 months of evaluation. Of these 11 pairs, nRTI or NNRTI resistance mutations were observed in the plasma virus of 4 source partners of 5 pairs. These comprised M41L/T69D/L210W, M184V, M41L/T215C, and K103N. The same resistance profiles were observed in the seroconverting partner. No primary protease inhibitor-associated mutations were observed in the source patients.

Transient Low-Level Viremia or "Blips"

Several abstracts dealt with the phenomenon of transient low-level viremia, so-called blips, among subjects with otherwise stable suppression of plasma viral load to below 50 copies/mL. Sklar and colleagues (Abstract 431) retrospectively evaluated subjects followed in the HIV Outpatient Study (HOPS) who had at least 2 consecutive measurements of plasma viral load below 50 copies/mL at least 2 months apart. Subjects were designated as high-level or low-level "blippers"; ie, with peak transient viremias of greater than 400 copies/mL or 400 or fewer copies/mL, or as those experiencing lasting viral rebound of greater than 400 copies/mL or 400 or fewer copies/mL. These groups were compared to a group who maintained stable suppression of plasma viral load below 50 copies/mL. Subjects were followed up for a mean of 517 days and a mean of 141 days from transient viremia.

Of the 481 subjects evaluated, 18 (3.7%) had lasting viremia of more than 400 copies/mL and 83 (17%) had lasting viremia of 50 to 400 copies/mL. Notably, 122 (25%) experienced only transient viremia (17.9 events/100 person-years). Among this group, 9 (7.4%) had more than 1 blip in viremia and 94 (77%) were low-level blippers. In 86 subjects (70%) the blips were single time point episodes of viremia. A majority (51%) had returned to levels below 50 copies/mL on the following measurement without a change in treatment. All episodes of transient viremia resolved by the third episode at the latest. A history of prior antiretroviral experience did not appear to be predictive of the incidence of blips or lasting viral rebound. The median first detectable plasma viral loads among transiently viremic and durably viremic patients were 96 and 201 copies/mL, respectively (P = .004). The changes in CD4+ cell count from baseline among subjects with stable suppression of plasma viral load, transient viremia, and lasting viral rebound at 50 to 400 copies/mL or lasting viral rebound above 400 copies/mL were +170, +205, +200, and +88/µL, respectively (P = .06).

Havlir and colleagues (Abstract 521) evaluated the HIV-specific immune responses in 2 groups of subjects: those with isolated single time point elevations above 50 copies/mL ("intermittent viremia" group, n = 11) and those with sustained suppression of HIV plasma viral load below 50 copies/mL (n = 10). These responses were compared to subjects with chronic infection treated for 1 year (n = 8), subjects with chronic untreated infection (n = 7), and subjects with early untreated infection (n = 4). Both early (Nef, Tat, and Rev) and late (Gag and Pol) HIV antigen responses were evaluated. Although HIV-specific immune responses could be demonstrated in treated patients with chronic disease, the presence of intermittent viremia, the baseline plasma viral load, the CD4+ cell count at the time of assay, and the change in CD4+ cell counts were not predictive of the frequency of these responses in multivariate analyses.

Greub and colleagues (Abstract 522) described the virologic outcomes of 604 of 1858 subjects (32.5%) experiencing transient low-level viremia after suppression of plasma viral load to below 50 copies/mL on the 2 (or more) preceding measures. Subjects were derived from the Swiss and Frankfurt HIV Cohort Studies. The most common outcome after a single episode of low-level viral rebound was a return to below 50 copies/mL on the next estimate, ie, a blip in viral load (n = 419 [70%]). Of these blips, 56% were low-level (50–100 copies/mL) and 43% were high-level (101–500 copies/mL) in nature. Therefore, the frequency of low-level viral rebound was 37.4 episodes per 100 person-years in this population. The incidence of virologic failure (a viral load above 500 copies/mL on 2 successive episodes) in optimally controlled subjects, those with blips, and those with sustained low-level viremia was 5.1, 7.9, and 21.7 per 100 person-years, respectively. For subjects whose plasma viral load did not return to below 50 copies/mL on the second or third determinations, the likelihood of return to below 50 copies/mL decreased and the likelihood of virologic failure increased over time. This was especially so if the second determination was above 100 copies/mL when only approximately 50% had return of the viral load to below 50 copies/mL. Using logistic regression models, subjects with a third value of 300 to 500 copies/mL were 80% less likely to have resolution of viral rebound. Notably, patients undergoing change in therapy were 2.5 times more likely to have resolution of low-level viral rebound.

Drug Resistance

Resistance to Stavudine and Zidovudine

There were several presentations evaluating the impact of nucleoside analogue mutations (NAMs) on virologic outcomes. Costagliola and colleagues (Abstract 450) evaluated the virologic outcomes in subjects with plasma HIV bearing 3 or more NAMs (1 of which was the 215F/Y mutation) who were treated with specific nRTIs. These were 143 nRTI- and protease inhibitor-experienced subjects who were in the standard of care arm of the NARVAL ANRS 088 trial. The mean baseline viral load and CD4+ cell count were 4.32 $\log_{10}$ copies/mL and 278/µL, respectively. For

Table **3.** Phenotypic and Genotypic Antiretroviral Drug Resistance Among Antiretroviral-Naive Individuals and in Primary HIV Seroconversion

Abstract No.	No. of Patients	Source	Genotype/Phenotype
754	197	Swiss Cohort, 1996-1999	Genotype
756	408	9 cities in North America	Phenotype (PhenoSense, ViroLogic, Inc.)
423	61	New York, NY and Montreal, Canada, 1999-2000 and compared with 1995-1998	Genotype (n = 61) Phenotype (n = 58) (PhenoSense, ViroLogic, Inc.)
436	103	US military recruits	Genotype Phenotype (PhenoSense, ViroLogic, Inc.)
426	12	Isolates with T215C/D/E or S from 143 drug-naive subjects	Genotype Phenotype, parallel growth (PhenoSense, ViroLogic, Inc.)

nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI indicates protease inhibitor.

subjects who had fewer than 3 versus those with 3 or more NAMs and who were treated with abacavir, stavudine, or didanosine, the mean changes in plasma viral load were –1.76 versus –0.39, –1.23 versus –0.26, and –1.25 versus –0.26 $\log_{10}$ copies/mL, respectively. While the observations with regard to abacavir and stavudine are not new, the findings in relation to didanosine-inclusive therapies are notable.

Cohen and colleagues (Abstract 444) evaluated the genotypic and virologic outcomes of 144 subjects pretreated with zidovudine (n = 99) or stavudine (n = 45) who switched to stavudine or zidovudine as part of the VIRA3001 study regimen. This study previously demonstrated the short-term benefits of phenotypic resistance testing in subjects failing their first protease inhibitor-inclusive regimen. Among those with prior zidovudine or stavudine experience the median CD4+ cell counts and plasma viral loads were 363 and 305/µL and 3.9 and 4.4 $\log_{10}$ copies/mL, respectively. Among those with prior zidovudine or stavudine experience, 70% and 69% had no NAMs, 9% and 20% had 1 NAM, and 13% and 16% had the T215Y/F mutation, respectively. The virologic outcomes were evaluated among zidovudine-experienced subjects who continued zidovudine (n = 19) or who switched to stavudine (n = 57) and among stavudine–experienced subjects who continued stavudine (n = 16) or who switched to zidovudine (n = 10). Seventy percent and 58% of those switching to zidovudine and to stavudine, respectively, also commenced an NNRTI. The proportion of subjects achieving a viral load below 400 copies/mL at 16 weeks of follow-up was 75% and 29% among those who switched to stavudine and those who switched to zidovudine, respectively (P = .034). Among those with no NAMs at baseline, only 2 (18%) of 11 stavudine-experienced and 27 (60%) of 45 zidovudine-experienced subjects achieved a plasma viral load below 400 copies/mL (P < .001) at follow-up.

Shulman and colleagues (Abstract 437) evaluated genotypic predictors of virologic outcomes in 46 subjects treated with stavudine monotherapy after 3 years of zidovudine monotherapy (ACTG 302). There were 8 responders (≥0.3 $\log_{10}$ copies/mL on-treatment reduction in viral load from baseline) and 23 nonresponders. The median baseline plasma viral loads were 4.2 and 4.7 $\log_{10}$ copies/mL in the responders and nonresponders, respectively (P = .01). The median CD4+ cell counts at baseline were 280 and 310/µL in the responders and nonresponders (P = .01), respectively. The median number of zidovudine-associated mutations was 1 and 2 in the responders and nonresponders (P = .09), respectively. Among the responders, 7 of 8 subjects had the K70R as their only zidovudine-associated mutation. No subject with more than 1 mutation had a virologic response to stavudine. Notably, codon changes at positions R83K and V90I were significantly more prevalent in responders than nonrespon-

Observations	Comments
In 1996, 1997, 1998, and 1999, the prevalence of drug resistance was 8.6%, 14.6%, 8.8%, and 5.0%, respectively. Mutations were observed in 10% of men and 2.6% of women and in 11.3%, 6.1%, and 13% of seroconverting homosexuals, heterosexuals, and injection drug users. The number of individuals infected with nonclade B HIV virus increased from 1996 (23%) to 1999 (35%); only one had virus with resistance mutations.	Causes of the relative decrease in frequency of drug resistance included the increase in infection with non-clade B virus and the increased frequency of suppression of plasma viremia <400 copies/mL.
Comparing 1996-1997 to 1999-2000, the percent of isolates with >10-fold resistance to nRTIs, NNRTIs, and to PIs rose from 2.7% to 8.2% (P = .03), from 1% to 7% (P = .007), and from 2% to 8% (P = .001), respectively. The frequency of isolates with resistance to ≥ 2 drugs rose from 0.4% to 5.3%, respectively.	The time to virologic suppression to <400 copies/mL was significantly greater in those with >10-fold resistance (P = .04).
The prevalence of primary PI and nRTI mutations was 26% for 1999-2000 and 16% for 1995-1998. The PI mutations M41I, V82A/T, I84V, or L90M were observed in 4 (6.5%) of 61. Eight isolates had nRTI mutations, 6 had NNRTI mutations and 1 isolate had both. Reduced drug susceptibility of >2.5-fold to any drug was observed in 22 (38%) of 58 and >10-fold in 4 (7%) of 58. Three isolates demonstrated phenotypic resistance to ≥2 drugs.	
Drug resistance mutations were observed in 21 (20%) of 103 isolates with 17 (16.5%) having intermediate/resistant phenotypes. The CD4+ counts and baseline viral load of those with and without drug-resistant isolates were 498 and 463 cells/μL and 4.7 and 4.5 $\log_{10}$ copies/mL, respectively. At 6 months of potent antiretroviral therapy (n = 80), the CD4+ cell count increases and the decreases in viral load were +269 and +170/μL and –3.2 and –2.7 $\log_{10}$ copies/mL, respectively.	Paradoxically greater CD4+ cell increases and reductions in plasma viral load were observed in those with drug resistance at baseline.
The prevalence of each mutation was: 215D, 4 (0.9%); 215C, 3 (0.7%); 215E, 1 (0.2%); and 215S, 4 (0.9%). The 215D/C change was observed in association with the M41L mutation. None of the isolates demonstrated zidovudine resistance. Drug-free replication capacity assays suggested the order of fitness was 215S > wild-type > 215C/D.	The authors suggest that in absence of zidovudine these mutants may be stable revertants from the T215Y mutation.

ders (P = 0.04). The authors suggest that the K70R mutation in isolation may not prevent a treatment response to stavudine.

Descamps and colleagues (Abstract 438) evaluated the impact of baseline genotypic zidovudine resistance in 153 subjects enrolled in the NOVAVIR ANRS 073 trial. This was a prospective, randomized study in which subjects with more than 6 months of prior experience with zidovudine, zalcitabine, and/or didanosine were treated with either zidovudine or stavudine in combination with lamivudine and indinavir and followed up for a median of 18 months. Subjects were naive to lamivudine, stavudine, and protease inhibitors. At baseline 96% of subjects had received dual-nRTI therapy and the median prior nRTI exposure was 19 months. The median CD4+ cell count and plasma HIV RNA level were 291/μL and 4.36 $\log_{10}$ copies/mL, respectively. At week 24 in the zidovudine and stavudine arms the gains in CD4+ cell counts were 175 and 195/μL, respectively (P = .29). Virologic failure (viral load >5000 copies/mL) was observed in 29 subjects, 15 in the zidovudine and 14 in the stavudine arms (P = .98). There was no difference in the prevalence of mutations at baseline in the 2 arms. There was no correlation between the number of nRTI mutations and baseline viral load. The proportion of patients with viral loads below 50 copies/mL at week 24 was significantly higher if the M41L and T215Y mutations were present at baseline compared to those without mutations at these codons, 87% versus 67% (P = .019). Furthermore, among subjects in the zidovudine arm, zidovudine resistance was associated with a significantly reduced risk of virologic failure (RR = .22; P = .02).

Lamivudine

D'Arminio-Monforte and colleagues (Abstract 447) evaluated the impact of the lamivudine resistance mutations E44D, V118I, and M184I/V on virologic outcomes in antiretroviral-naive subjects in the ICONA cohort who were receiving lamivudine-inclusive potent antiretroviral regimens. The median CD4+ cell counts and plasma viral loads were 212/μL and 4.92 $\log_{10}$ copies/mL, respectively. Lamivudine resistance mutations were observed at baseline in 12 subjects. The E44D, V118I, and M184V mutations were observed in 1 (0.4%), 9 (3.6%), and 2 (0.8%) subjects, respectively. The numbers of subjects who achieved a plasma viral load below 500 copies/mL at week 32 who had no resistance mutations at codons 44 and 118 or who had either the E44D or V118I mutations were 152 (63%) and 10 (100%), respectively. Of the 2 subjects with the M184V mutations, one achieved virologic suppression. The authors suggest that the single mutations at positions E44D or V118I do not seem to impair virologic response to lamivudine-containing potent regimens. However, this should be interpreted with caution given the limited number of subjects studied.

Observations on Abacavir, Tenofovir, and NNRTI Therapies

Melby and colleagues (Abstract 448) described the evolution of resistance to abacavir in subjects failing an abacavir-combination zidovudine-lamivudine regimen. Subjects were enrolled in study CNA3005, a double-blind placebo-controlled randomized trial comparing combination zidovudine-lamivudine with either abacavir or indinavir. At week 96, 48 (15%) of 282 subjects had experienced virologic failure in the abacavir arm, among whom 61% had the M184V mutation in isolation and 23% had no nRTI-associated mutations. The proportion of subjects with M184V plus any nucleoside analogue–associated mutation increased over time, being 10% of 39 subjects at 0 to 8 weeks of virologic failure and 56% of 16 subjects at weeks 41 to 48. Four to 6 months after first genotype, 75% of subjects had isolates that were wild-type or had the M184V mutation only. At 96 weeks the median reductions in viral load from baseline were 1.5 and 1.6 $\log_{10}$ copies/mL in all 40 subjects with virologic failure and in the 15 subjects with M184V plus any NAMs, respectively.

Lanier and colleagues (Abstract 254) compared the relative discriminatory values of 2.5- and 4.5-fold cutoffs to define phenotypic resistance to abacavir as predictors of virologic outcomes in 140 subjects who had participated in 4 trials in which abacavir was added to stable background therapy. The median CD4+ cell count and plasma viral load were 391/µL and 3.8 $\log_{10}$ copies/mL, respectively. The endpoint was defined as a 0.5-$\log_{10}$ copies/mL reduction in plasma viral load or achieving a viral load below 400 copies/mL after a median of 24 weeks of follow-up. The presence of 4 or more nRTI resistance mutations was associated with a 5.2-fold reduced likelihood of reaching the virologic endpoint (P = .037). The likelihood of a response was significantly reduced in the setting of a baseline 4.5-fold or greater reduction in sensitivity relative to wild-type virus (P < .001). Response to abacavir was severely reduced (<20%) in the 14 subjects with a 7-fold or greater reduction in sensitivity at baseline.

Miller and colleagues (Abstract 441) described the virologic outcomes at 24 and 48 weeks of follow-up among 54 subjects who had 300 mg tenofovir added to stable background therapy and related these to the baseline genotype and phenotype. Study 902 was a placebo-controlled, double-blinded dose-ranging study. At baseline 94%, 57%, and 32% of subjects had nRTI-, protease inhibitor-, and NNRTI-associated mutations, respectively. At weeks 24 and 48 the average changes in the plasma viral load were –0.58 and –0.62 $\log_{10}$ copies/mL, respectively. Significant averaged reductions in plasma viral loads at 24 weeks were observed in subjects with M184 wild-type (22), the M184V mutation (32), and the M184V mutation but no zidovudine mutations (9); these were –0.48, –0.65, and –0.91 $\log_{10}$ copies/mL, respectively. Diminished virologic responses were significantly associated with reduced baseline tenofovir susceptibilities (P = .007).

The patterns of NNRTI cross-resistance were evaluated by Delaugerre and colleagues (Abstract 449) in 3 populations: 39 subjects on a failing efavirenz-based regimen, 46 subjects on a failing nevirapine-based regimen, and 19 subjects on a failing efavirenz-based regimen after nevirapine failure. The incidence of NNRTI resistance mutations was high, 102 of 104 (98%). The K103N mutation was observed in 51%, 25%, and 36% of subjects in the efavirenz, nevirapine, and nevirapine-then-efavirenz treatment groups, respectively. The Y181C mutation was observed in the nevirapine-only treatment group (18%). In the nevirapine failure group the incidence of genotypic coresistance to efavirenz was significantly higher in those concurrently treated with zidovudine or stavudine versus those not receiving nucleoside analogues, 33 (85%) of 39 and 2 (40%) of 5 (P = .02). These data do not support the sequential use of the currently approved NNRTIs.

Observations on Lopinavir/Ritonavir–Inclusive Therapies

Brun and colleagues (Abstract 452) described the phenotypic and genotypic HIV resistance profiles in 5 protease inhibitor–experienced subjects with virologic rebound on lopinavir/ritonavir inclusive therapies. Prior to lopinavir/ritonavir therapy all subjects had at least 4 of the 11 protease mutations specifically associated with resistance to lopinavir. At viral rebound each of the viral isolates remained resistant to or developed resistance to indinavir and ritonavir coincident with the development of phenotypic lopinavir resistance. However, all rebound viruses remained fully susceptible or demonstrated only modestly reduced susceptibility to amprenavir (≤8.5-fold reduced susceptibilities) in the setting of high-level lopinavir resistance. Notably, the rebound isolates in the 3 subjects with no prior saquinavir exposure remained fully susceptible to saquinavir. The correlations between resistance to lopinavir and ritonavir, indinavir, saquinavir, and amprenavir were R^2 = .82, 0.67, 0.27, and 0.21, respectively. Isolates with eight or more mutations associated with lopinavir resistance demonstrated median reductions in susceptibilities of 44-fold to lopinavir and 6-fold to amprenavir. Notably, the 2 lopinavir-resistant isolates tested for susceptibility to tipranavir remained fully susceptible to this drug. Data were presented for 1 patient experiencing virologic failure at 70.5 weeks (approximately) of lopinavir/ritonavir-based therapy. The plasma virus demonstrated 25-fold reduced susceptibility to lopinavir but was fully susceptible to amprenavir. This individual has successfully achieved sustained virologic suppression (<400 copies/mL) up to last measurement at 32 weeks on amprenavir (1200 mg bid)/ritonavir (200 mg bid)/abacavir/stavudine therapy.

Bernstein and colleagues (Abstract 453) described the 24- and 48-week outcomes for study M98-863, a randomized double-blind placebo-controlled trial of combination stavudine/lamivudine with either nelfinavir (n = 326) or lopinavir/ritonavir (n = 326) in antiretroviral-naive subjects. By ITT analysis (M = F) 52% and 67% of subjects in the nelfinavir and lopinavir/ritonavir arms, respectively, achieved viral loads below 50 copies/mL at week 48 (P < .001). Genotypic data were available for 37 of 58 subjects in the lopinavir/ritonavir arm and 76 of 102 subjects in the nelfinavir arm who had viral loads above 400 copies/mL between weeks 24 and 48. For subjects in which nelfinavir was failing, the D30N and/or L90M mutations were observed in 25 (33%), while no primary protease inhibitor mutations were observed in the 37 subjects failing lopinavir/ritonavir (P < .001). Notably, the M184V mutation was observed in 15 (41%) of lopinavir/ritonavir failures and 62 (82%) of nelfinavir failures. Adherence as measured by pill counts of active drug was not statistically different between the 2 groups with drug treatment failure. However, drug treatment responders (n = 431) had significantly greater adherence than nonresponders (n = 160) (P < .001). None of the 19 subjects with

genotypic nelfinavir resistance experienced on-study resuppression of viral load to below 400 copies/mL. However, 22 (85%) of 26 subjects in the lopinavir/ritonavir arm had spontaneous resuppression at least once in follow-up. The occurrence of virologic failure in the absence of primary protease mutations is not a novel observation. However, the relatively higher incidence of protease wild-type genotype and lower incidence of the lamivudine mutation M148V in the lopinavir/ritonavir arm relative to the nelfinavir arm observed in this study are notable.

The Relationship of Trough Amprenavir Drug Levels and Evolution of Resistance

Elston and colleagues (Abstract 465) described differential genotypic evolutionary pathways of amprenavir resistance in relation to trough plasma amprenavir levels. The I50V, I84V, V32I+I47V, and I54L/M mutations were associated with mean reductions in amprenavir susceptibilities of approximately 23-, 13-, 8-, and 5-fold, respectively. The I50V mutation occurred in 4 subjects with a median trough amprenavir level of 517 ng/mL, whereas the I54L mutation occurred in 4 subjects with a median trough level of 164 ng/mL (P = .015). Parallel growth curves of HXB-2 and isolates bearing the I54L or I50V mutations in the absence of drug demonstrated modest compromise of the I54L-bearing isolates and severe impairment of the I50V-bearing isolates. These data suggest that higher plasma amprenavir trough levels favor the emergence of phenotypically more resistant but potentially less fit viruses bearing the I50V mutation.

Genotypic and Phenotypic Predictors of Outcome

The 24-week analysis of the Havanna trial was presented by Tural and colleagues (Abstract 434). This prospective, multicenter, randomized study evaluated the relative impact of genotyping and/or expert advice in the redesign of a failing antiretroviral regimen (n = 274). The panel of experts comprised clinicians and virologists with access to all relevant medical data. At baseline the mean CD4+ cell count and plasma viral load were 390/µL and 4.0 $\log_{10}$ copies/mL, respectively. The mean times on antiretroviral therapy and protease inhibitor therapy were 4.4 and 2.0 years, respectively. The proportion of subjects never having received a protease inhibitor was 10%. At 24 weeks the percentages of subjects with viral loads below 400 copies/mL (early dropouts excluded) in the genotyping and no genotyping arms were 57.5% and 42.4%, respectively (P = .01); in the expert advice and no expert advice arms, they were 59% and 41% (P = .003), and for those receiving genotyping with expert advice versus those receiving only standard of care, they were 69% and 36.4%, respectively (P = .001). Thus, within this study population the application of genotyping and/or expert advice was significantly better than the standard of care alone.

The final 6-month follow-up data from the ARGENTA trial were presented by De Luca and colleagues (Abstract 433). In this study 174 subjects in whom HAART-based therapy was failing had treatment decisions determined by genotyping plus expert panel decisions (n = 85) or by standard of care plus expert panel decisions (n = 89). Patient adherence was assessed by self-reported questionnaire. At baseline the median CD4+ cell count and plasma viral load were 265/µL and 4.25 $\log_{10}$ copies/mL, respectively. The percentages of subjects with failure of 1, 2, or at least 3 or more prior HAART regimens were 47%, 28%, and 25%, respectively; 41% of subjects had experience with all 3 available classes, and 23% had a history of a plasma viral load below 500 copies/mL. The median number of resistance mutations was 7 at entry, being 8 in the genotyping arm and 7 in the standard of care arm (P = .03). The percentage of patients with plasma viral loads below 500 copies/mL in the standard of care and genotyping arms at 3 and 6 months were 12% and 27% (P = .02) and 17% and 21%, respectively (P = NS). The CD4+ cell count responses were not significantly different between the 2 arms. At 6 months the CD4+ cell count changes in the adherent (>95%) and nonadherent groups were +62 and −13/µL, respectively (P < .01). At 6 months the factors significantly predictive of a plasma viral load below 500 copies/mL were the baseline viral load (OR = 0.4, per $\log_{10}$ increase), failing a first or second HAART regimen (OR = 5.6), and a prerandomization history of a viral load below 500 copies/mL. In this population genotypic testing provided only a modest short-term benefit beyond expert panel advice in terms of achieving a plasma viral load below 500 copies/mL. Patient-reported adherence strongly influenced CD4+ cell count outcomes at 6 months.

Katzenstein and colleagues (Abstract 435) evaluated baseline nRTI, NNRTI, and protease inhibitor drug susceptibilities (PhenoSense, ViroLogic, Inc.) and other baseline variables as predictors in patients having a plasma viral load below 50 copies/mL at 16 (n = 131) and 48 (n = 127) weeks of follow-up within ACTG 364. This study previously demonstrated the superiority of combination nelfinavir and efavirenz over nelfinavir or efavirenz therapies in nRTI-experienced subjects. At baseline the median CD4+ cell count and plasma viral load were 336/µL and 4.17 $\log_{10}$ copies/mL, respectively. Exposure to more than 52 weeks of zidovudine, didanosine, zalcitabine, stavudine, or lamivudine was present in 100%, 56%, 31%, 6% and 62% of subjects analyzed, respectively. Two models of phenotypic susceptibility scoring (PSS) were evaluated. In each the total score for each subject was the sum of the score for each of the drugs used in the patient's study regimen. In the dichotomous model a drug was scored as susceptible = 1, resistant = 0 (>2.5-fold IC_{50}) and in the continuous model partial resistance scoring was allowed with fold changes of more than 2.5 to less than 10 being scored as between 0 and 1. At week 16, only higher baseline viral load (RR = .35, P = .001) and the number of new drugs (RR = 2.25, P = .003) were predictive of reaching the study endpoint. At week 48, only the number of new drugs (RR = 3.28, P < .001) and the continuous PSS (RR = 2.37, P = .009) were significant predictors of outcome. The authors note that with the use of stavudine- and didanosine-containing regimens, continuous measures of resistance enhanced the predictive values of the low-level resistance typically observed with these drugs.

Graham and colleagues (Abstract 524) retrospectively compared the values of the plasma HIV drug resistance genotype and the actual and virtual phenotypes in predicting failure to reach a plasma viral load of less than 400 copies/mL and less than 50 copies/mL at 16 weeks among 191 subjects in the VIRA3001 trial. They demonstrated a high concordance between the virtual and actual phenotypes, with correlation coefficients ranging from 0.86 to 0.89. In multivariate models the virtual phenotype was predictive for failure to have a plasma viral load of below 400 and below 50 copies/mL at follow-up. Notably, the actual phenotype was significantly predictive only for failure to reach below

400 copies/mL. A simple rules-based genotypic scoring system was inferior to either type of phenotype, but this should be interpreted with caution. The authors note that the resistance cutoffs for the virtual and actual phenotypes were different. The virtual phenotype employed cutpoints derived from the evaluation of biologic variation in resistance among drug-naive subjects. This may have enhanced detection of resistance to both stavudine and saquinavir.

Leigh Brown and colleagues (Abstract 424) evaluated the association between differences in protease sequences and modest differences in protease inhibitor susceptibilities as determined by the ViroLogic PhenoSense assay. For the purposes of this study a 2.0-fold cutoff on the phenotypic assay was used to define reduced susceptibility. Plasma virus was derived from 164 subjects who had seroconverted between 1997 and 1998 and who had never received antiretroviral therapy. For ritonavir, changes at codons 62 and 82 were associated with modest resistance; eg, 62V/82I (n = 3) was associated with 3.2-fold reduced ritonavir susceptibility. For nelfinavir, the groups 36I/57K/63P, 15V/77I/93I, and 15V/41K/63A/82I were associated with 3.0-, 2.9-, and 2.5-fold reduced susceptibilities to nelfinavir, respectively. The authors speculate that these groups of mutations may have relevance to subjects treated with nelfinavir-inclusive therapies.

Mechanisms of Resistance to T-20

Mink and colleagues (Abstract 474) evaluated mechanisms of resistance to T-20, a fusion inhibitor. This drug specifically inhibits the interaction of 2 heptad repeat sequences, HR1 and HR2 of the HIV envelope glycoprotein gp41 that is required for virus-CD4+ cell fusion. T-20 is a 36-amino acid synthetic peptide derived from HR2 which targets the HR1 domain. The authors note that the binding affinity to HR1 domains containing mutations associated with T-20 resistance correlated with T-20 phenotypic susceptibilities. For example, the observed binding affinities (B) and IC_{50} values associated with the HR1 QHQ versus the QQQ sequences were 0.10 and 4.33 (B_{50}, µg/mL) and 0.009 and 0.256 (IC_{50}, µg/mL), respectively. These data highlight the relationship between structural changes at the binding domain and resistance to T-20.

Natural History After Virologic Failure

Deeks and colleagues (Abstract 428) defined factors associated with clinical progression to a new AIDS-defining illness or death in a well-described cohort of 289 subjects with confirmed virologic failure on a protease inhibitor-inclusive regimen. At onset of virologic failure the median CD4+ cell count and plasma viral load were 124/µL and 4.74 $\log_{10}$ copies/mL, respectively. The median follow-up time was 38.5 months. After onset of virologic failure there were 55 events in 567.3 person-years of observation. During follow-up 47 (16%) of those experiencing virologic failure died compared to 19 of 193 (9%) in those with stable suppression of plasma viremia below 500 copies/mL. The probability of clinical progression after 2 and 4 years of continuous virologic failure on a protease inhibitor-based regimen was 18% and 41%, respectively. In uni- and multivariate models clinical progression during virologic failure was predicted by the most recent level of viremia (proximal viral load >4.37 $\log_{10}$ copies/mL, RR = 4.3, P = .02), by the most recent CD4+ cell count, (proximal CD4+ cell count 42–122 and <42 cells/µL; RR = 2.9 [P = .02] and RR = 6.3 [P < .01]), respectively, and by the difference in viral load from a pretherapy set point (difference less than –0.32; RR=4.2 [P = .001]). Most recent CD4+ T cell count appeared to be the strongest predictor of disease progression.

The relative rates of accumulation of CD4+ cells in subjects experiencing varying degrees of virologic suppression on protease inhibitor-based therapies were evaluated by Le Moing and colleagues (Abstract 432). Subjects (n = 988) were enrolled in the APROCO study. The median follow-up time was 23 months. At baseline the median CD4+ cell count and plasma HIV RNA level were 290/µL and 4.4 $\log_{10}$ copies/mL, respectively. At month 4 80% of subjects achieved a plasma viral load below 500 copies/mL. The rate of accumulation of CD4+ cells was greatest in those with sustained suppression of viremia compared to those with loss of suppression after month 4 and those who did not achieve suppression of plasma viremia by month 4. An inflection was observed in the long-term CD4+ cell count slope of those experiencing onset of virologic failure after month 4 and was related to the absolute level of viremia achieved. The slope was +7.4 cells/month for those maintaining virologic suppression. The slope remained positive for those with rebound below 10,000 copies/mL (+4.8 cells/month) but was negative in those with more than 10,000 copies/mL (–2.7 cells/month).

Treatment Interruptions

Tebas and colleagues (Abstract 355) retrospectively evaluated the CD4+ cell count decay slopes among 31 subjects who interrupted therapy for a mean of 50 weeks (20–119 weeks) and who had preceding stable suppression of plasma viremia below 500 copies/mL for a mean of 20 weeks (10–37 weeks). The median CD4+ cell count at treatment interruption was 635/µL. A mean steady-state decay of 16 cells/µL per month was observed. The only predictor of CD4+ cell count slope decay was the magnitude of change prior to interruption (r = –0.53, P = .008). The rate of decay was greatest during the first 6 months of therapy. At follow-up, 55% of subjects had a viral load within 0.5 $\log_{10}$ copies/mL of their pretreatment set point. The authors suggest that CD4+ cell-driven treatment strategies including treatment "pulses" may merit further evaluation.

Deeks and colleagues (Abstract 292) presented data on salvage outcomes in a subset of subjects from a cohort with established failure of a protease inhibitor-based regimen. In the 22 subjects studied the median duration of failure of protease inhibitor-based therapy was 36 months. The median CD4+ cell count and plasma viral load were 217/µL and 4.6 $\log_{10}$ copies/mL, respectively. At baseline, there were 56- and 10-fold median reductions in susceptibilities to the on-treatment protease inhibitor and to abacavir, respectively. The median duration of treatment interruption was 26 (range, 16–30) weeks. The median increase in plasma viral load and decrease in CD4+ cell count was 0.74 $\log_{10}$ copies/mL and 95/µL, respectively. The plasma virus in 18 of 19 subjects demonstrated a reversion of phenotypic protease inhibitor resistance to wild-type during the treatment interruption. One episode of P*neumocystis carinii* pneumonia and 1 episode of ITP were observed during treatment interruption. Twenty-two subjects underwent salvage therapy, 19 with a salvage regimen comprising 2 nRTIs, ritonavir with a second protease inhibitor, plus an NNRTI. At 24 weeks of follow-up the median decrease in plasma viral load and increase in CD4+ cell count were 3.0 $\log_{10}$

copies/mL and 82 cells/μL, respectively. At follow-up on salvage therapy 15 of 22 had CD4+ cell counts greater than 90% of their preinterruption level. Eleven of 22 subjects had exposure to 1 new drug class as part of their salvage regimen as either an NNRTI (9) or T-20 (2). All subjects with exposure to a new drug class had plasma viral loads below 200 copies/mL, and of those with no new drug class exposure, 3 of 11 had plasma viral loads below 200 copies/mL. One patient had rebound of plasma viral load after successful suppression with virus genotypically similar to the preinterruption genotype.

The virologic and CD4+ cell count outcomes among 481 subjects experiencing extended on-treatment virologic failure were presented by Sabin and colleagues (Abstract 293). Subjects were derived from a multicohort collaborative study and were failing stable drug regimens of at least 3 antiretrovirals at entry. The prior nadir CD4+ cell count and peak viral load were 90/μL and 5.48 $\log_{10}$ copies/mL, respectively. The median number of prior antiretrovirals used was 6 (3–15). The median CD4+ cell count at treatment interruption, at follow-up, and change post-interruption was 203, 117, and –53/μL, respectively (P = .0001). The median plasma viral load at interruption, at follow-up, and change post-interruption was 4.86, 5.26, and +0.26 $\log_{10}$ copies/mL, respectively (P = .0001). Multivariate analysis demonstrated that both the nadir and entry CD4+ cell counts and the entry viral load were significantly associated with the change in CD4+ cell count during the treatment interruption. Antiretroviral therapy was reinitiated in 445 subjects with a median of 3 drugs. At 28 weeks of follow-up approximately 60% of subjects achieved a plasma viral load of below 500 copies/mL. The factors predictive of reaching a plasma viral load below 500 copies/mL included the baseline CD4+ cell count (RR = 1.06, P = .03), baseline viral load (RR = 0.57, P = .001), CD4+ cell count at end of treatment interruption (RR = 1.09, P = .0004), viral load at end of treatment interruption (RR = 0.83, P = .03), the number of drugs used (RR = 1.22, P = .001), and a history of a viral load less than 500 copies/mL (RR = 1.93, P = .003).

Grant and colleagues (Abstract LB3) described the dynamic interactions of in vivo viral fitness, in vitro replication capacity, genotypic resistance, and plasma viral rebound in 12 subjects with established failure of a protease inhibitor–based regimen undergoing a treatment interruption. Subjects had experienced 12 or more months of on-treatment virologic failure and had plasma viral loads higher than 2500 copies/mL. Post-interruption plasma viral loads were estimated every week for 12 weeks, then every other week. At follow-up, the median changes in CD4+ cell count and viral load were –51/μL and +0.78 $\log_{10}$ copies/mL, respectively. Reversion from protease inhibitor–resistant to protease inhibitor–sensitive phenotype was observed in 12 of 12 subjects after a median of 6.5 weeks post–treatment interruption. The ratio of wild-type to mutant virus was estimated by differential hybridization of reverse transcriptase polymerase chain reaction (PCR) product to probes specific for 16 loci (mutant and wild-type) in the HIV protease and reverse transcriptase (Bayer Diagnostics). In all subjects 4 to 9 loci were evaluated. The assay has a differential detection range of 3% to 92%. The calculated median relative in vivo fitness difference between wild-type and mutant virus was 13.9 (3.3–36.1). This correlated with increases in plasma viral load post–treatment interruption (= 0.62, P = .03). The percent wild-type to mutant virus prior to treatment interruption was derived by extrapolation from post-interruption dynamics and ranged approximately from 1.6% to 0.015%. This correlated negatively with the wild-type/mutant fitness difference post–treatment interruption (= –0.86, P = .0003). In 3 subjects the analysis suggested approximately 1% wild-type preinterruption. From baseline to follow-up the changes in the in vitro replication capacity correlated well with both the changes in in vivo fitness (= 0.82, P = .001) and the increase in plasma viral load post-interruption (= 0.80, P = .002). These data further advance our understanding of the complex viral dynamics existing during protease inhibitor–associated treatment failure and treatment interruptions.

Hance and colleagues (Abstract 293) presented a detailed examination of minority plasma virus populations in 2 subjects undergoing treatment interruption of a failing protease inhibitor–based regimen. Detection of minority species was by cloning from bulk PCR products and by quantitative real-time PCR specific to protease codons 82 and 90. Plasma samples from patients 1 and 2 were evaluated at 5 and 3 months, respectively, at which time there was reversion of genotypic protease inhibitor resistance to wild-type by population-based sequencing. In patient 1 at 5 months post–treatment interruption, the V82A mutation was present in 3 of 176 clones and 3% of the bulk PCR product. In patient 2, at 3 months post–treatment interruption, the L90M mutation was present in 5 of 131 clones and 4% of bulk PCR product. Prior to treatment interruption, patient 1 had plasma HIV protease sequence demonstrating the L10I, G48V, I54V, V71I, and V82A mutations. In this patient cloning demonstrated isolates with 2, 3, 4, and 5 of the protease inhibitor resistance mutations present in the preinterruption plasma virus, suggesting that the viruses intermediate in the evolution of the fully resistant isolate were present in plasma and were replication-competent.

Pharmacology

Presentations highlighting various pharmacologic aspects of antiretroviral therapy were a prominent feature at the conference. The major themes included (1) the elucidation of pharmacologic properties of new agents (outlined in the preceding sections); (2) the characteristics and enhancement of the intracellular levels of antiretroviral agents; (3) drug-drug interactions; (4) compartmental pharmacokinetics and efficacy of antiretroviral drugs; (5) drug transporters; and (6) therapeutic drug monitoring.

Intracellular Characteristics of Antiretroviral Drugs

Several studies described the intracellular properties of antiretroviral agents, specifically relating to the accumulation of the parent drug, their active metabolites, or means of enhancing their levels. Work presented at a previous Conference suggested that prior zidovudine therapy might interfere with the intracellular activation/phosphorylation of subsequently administered stavudine. In contrast, and arguing that the sequence of nucleoside analogue initiation had no such effect, Parsons and colleagues (Abstract 257) at the 2001 Conference proposed that there were no significant differences in zidovudine or stavudine triphosphate levels in cells obtained from zidovudine- or stavudine-naive or experienced (>12 months) patients. Moreover, these levels were similar in the cells of patients responding to therapy or taking failing therapy. It was also noted that zidovudine triphosphate levels were significantly lower in zidovu-

dine or stavudine-experienced versus stavudine-naive subjects. Abacavir phosphorylation was unaffected by prior zidovudine or stavudine experience.

Further describing the intracellular characteristics of abacavir, Harris and colleagues (Abstract 746) reported the finding that the measured intracellular half-life (>12 h) of the active form of abacavir (carbovir triphosphate) supported a 600 mg once-daily dosing schedule of this compound. Finally, in the CHARM phosphorylation substudy, Back and colleagues (Abstract 747) demonstrated that hydroxyurea in combination with abacavir-lamivudine-zidovudine does not alter drug/endogenous triphosphate levels for abacavir or lamivudine, although carbovir triphosphate/dGTP levels were increased in those individuals who received the above regimen with nevirapine.

Using another inhibitor of endogenous triphosphate formation, mycophenolic acid (MPA), Margolis and colleagues (Abstract 351) demonstrated that adjuvant MPA could increase carbovir triphosphate/dGTP ratio by week 2 at doses which are half of those used in organ transplantation. The same group reported that MPA could enhance the in vitro antiviral effects of abacavir, tenofovir, and didanosine in a dose-dependent manner to both wild-type and drug-resistant HIV-1 strains (Hossain and Margolis, Abstract 307). For example, the tenofovir IC_{50} for a virus harboring the K65R mutation decreased from 6.37 µmol/L to 0.17 µmol/L with the addition of MPA.

Describing the differential intracellular accumulation of protease inhibitors, Khoo and colleagues (Abstract 258) presented the mean ratios of AUC intracellular/AUC plasma of the currently available agents in this class. Based on these calculations, these levels from highest to lowest were nelfinavir (6.21), saquinavir (4.15), ritonavir (1.18), indinavir (0.42). In this study, the addition of ritonavir did not enhance the intracellular level of saquinavir. However, contrasting with this finding, Dowdy and colleagues (Abstract 737) found that ritonavir appeared capable of reversibly inhibiting CD4+ lymphocyte P-glycoprotein activity as measured by a dye efflux inhibition assay, thus suggesting that coadministered ritonavir could theoretically increase the penetration of other protease inhibitors intracellularly and in sequestered body compartments.

Drug-Drug Interactions

A number of presentations described the pharmacokinetic interactions of antiretroviral agents. These are selectively summarized in Tables 4 and 5. The importance of these interactions is exemplified by the growing body of evidence that suggests that protease inhibitor and NNRTI drug levels correlate with both clinical efficacy and safety.

Compartmental Pharmacokinetics and Efficacy of Antiretroviral Drugs

As in prior years, several presentations addressed concerns over potential latent viral reservoirs despite virologic response to active combination therapy in the plasma compartment. As such a phenomenon might be related to the loss of true combination therapy in body compartments that pose a pharmacologic barrier to 1 or more drugs in a regimen, body compartments have been studied for differential pharmacokinetics and/or residual detectable virus in the face of plasma viral suppression. The most studied compartments are the central nervous system/cerebrospinal fluid, the genitourinary tract, the gastrointestinal tract, and lymphoid tissue.

Gastrointestinal Mucosa. Elliott and colleagues (Abstract 388) demonstrated persistently detectable HIV-1 DNA in serial rectosigmoid biopsies of 9 infected subjects who, after receiving combination antiretroviral therapy, had plasma HIV-1 RNA below 50 copies/mL for at least 3 months. Over a 15-month follow-up period, mucosal HIV-1 RNA was either intermittently or consistently detectable in 2 of 9 and 3 of 9, respectively. Mucosal HIV-1 DNA was detected in all patients with higher levels, correlating with longer periods of time prior to the initiation of HAART (mean of 69 months, $R = 0.737$, $P = .02$), but not with time on HAART or years of HIV infection. Therefore, from this study, it appears that HAART does not facilitate the decay of the mucosal reservoir. In another study demonstrating residual virus in the gastrointestinal mucosa of individuals with undetectable plasma HIV-1 RNA, Collis and colleagues (Abstract 396) showed that HIV shedding was present from either the pharyngeal or rectal mucosa in one third of plasma-suppressed patients.

Genitourinary Tract. In an examination for latent infection in seminal cells obtained from HIV-infected subjects with plasma virologic response to HAART, Nunnari and colleagues (Abstract 391) found that, in contrast to peripheral blood lymphocytes, 2-LTR circular DNA, suggestive of cryptic viral replication, was not detectable. The authors suggested that, despite active antiretroviral therapy in the plasma compartment to less than 50 copies/mL, the absence of 2-LTR circular DNA in seminal cells (ie, the lack of cryptic viral replication) implies that proviral latency is the major mechanism of viral persistence in the seminal compartment. Examining other tissue types in the genitourinary tract for latent viral reservoirs, Winston and colleagues (Abstract 392) demonstrated persistent HIV-1 RNA in renal epithelial cells in patients on combination antiretroviral therapy with plasma HIV-1 RNA levels below 50 copies/mL. Relatedly, Paranjpe and colleagues (Abstract 397) noted that while the viral decay in semen and plasma collected from 8 HIV-infected subjects following the initiation of HAART had similar first phase viral decay half-lives (1.8 ± 0.25 and 1.4 ± 0.6 days, respectively), second phase decay in semen was much slower than that in plasma.

Pereira and colleagues (Abstract 749) presented the results of ACTG 850, a 24-week randomized placebo-controlled substudy of 31 HIV-infected men receiving amprenavir with or without lamivudine/zidovudine. Blood and semen specimens were collected after observed medication doses at weeks 8 (early) and 24 (late) to assess the pharmacokinetic correlation between these 2 compartments. Both amprenavir early and late compartmental semen-blood ratios were 0.2, while in contrast, lamivudine ratios were 1 or greater, suggesting that unlike amprenavir, this drug readily enters the semen, is not dependent on blood concentrations, and possibly accumulates through active uptake transports (ie, nucleoside and organic acid transporters). Zidovudine also had median early and late compartmental ratios of 1or greater, but was noted to have a biphasic distribution, possibly due to an initial accumulation through passive diffusion followed by a later effect from slowed exit transport. In terms of compartmental virologic efficacy, approximately half of amprenavir monotherapy recipients had both seminal and blood responses at 8 weeks, although there were discordant responses in 7 subjects who had suppression in the blood compartment but detectable virus in their semen. Those with viral suppression in the semi-

nal compartment had significantly higher amprenavir semen levels.

In an analogous study, Reddy and colleagues (Abstract 750) reported the pharmacokinetics and antiviral effects of efavirenz-containing combination regimens in semen. In this 30- to 40-day study of both efavirenz-experienced and -naive subjects, median C_{min} blood and semen concentrations were 2.07 to 2.44 and 0.08 mg/L, respectively. All measured efavirenz concentrations were above the protein-corrected IC_{90} for wild-type HIV-1. Discordant viral suppression between blood and semen was seen in 25% of subjects, but did not seem to correlate with blood or semen efavirenz concentrations.

Three studies presented the different virologic characteristics in the female genital tract versus those in plasma in response to antiretroviral therapy. In the study by Cu-Uvin and colleagues (Abstract 718), 18 antiretroviral-naive and 8 experienced subjects were followed up for over 1 year to determine compartmental properties of virologic failure. Of the 5 subjects failing therapy, 3 had both plasma and cervical viral load rebound above 400 copies/mL and 2 had rebound only in plasma. All patients with undetectable plasma HIV-1 RNA levels also were undetectable in cervicovaginal lavage fluid. De Pasquale and colleagues (Abstract 446) found that drug resistance mutations found in plasma HIV-1 isolates could differ from those found in cervicovaginal lavage fluid. Of 7 women with virologic failure, 5 had mutations not found in their plasma in both the protease (codons 46, 54, 82, 84, and 90) and reverse transcriptase genes (codon 184). Sequence polymorphisms also varied between the 2 compartments. This is in contrast to the viral isolates from drug-naive women, where such divergence was not seen.

Similarly, Yamamura and colleagues (Abstract 719) found genotypic differences between the plasma and genital tract isolates. In 4 of 5 samples of paired plasma and vaginal swabs, the plasma portion showed higher numbers of mutations at both drug resistance and nonresistance sites, with a mean number of 9.6 in plasma versus 5.6 in the vaginal fluid viral isolates. In addition to emerging independent of plasma mutants, the emergence of drug-resistant mutants was delayed in the vaginal compartment.

Central Nervous System. Several studies described the relationship between virologic responses in plasma versus cerebrospinal fluid (CSF) and factors that appear to influence the response to antiretroviral therapy in the CSF compartment. Included among predictors of CSF response were the treatment status of the patient (naive > experienced and less prior antiretroviral therapy) and antiretroviral drug characteristics (greater CSF availability).

Analyzing a database comprised from 900 samples of 464 patients, Letendre and colleagues (Abstract 616) showed several CSF virologic response characteristics. CSF HIV-1 RNA levels were approximately 1.5 $\log_{10}$ copies/mL lower than plasma levels. Higher CSF HIV-1 RNA levels were associated with higher plasma RNA ($R = .60$), CSF pleocytosis (≥5 white blood cells; $R = .40$, $P < .001$), elevated CSF protein ($R = .26$), lower blood CD4+ lymphocytes ($R = -.20$) and hematocrit ($R = -.06$, $P = 0.03$), and absence of antiretroviral therapy ($P < .001$). Subjects taking nRTI- and NNRTI-containing regimens more frequently suppressed their CSF viral levels. Patients only taking nRTIs or no nRTIs were approximately twice as likely to have elevated CSF HIV-1 RNA levels (30% vs 18%; OR, 1.98; $P = .007$). In a linear regression analysis, the NNRTI benefit remained significant. The same group further proposed that the measurement of antiretroviral drug CSF concentration/IC_{50} ratio might be a better predictor of CSF virologic efficacy than measuring CSF drug concentrations alone (Abstract 614).

Antinori and colleagues (Abstract 613) also sought to define factors that might influence CSF virologic responses to therapy. The authors studied 75 patients (37% antiretroviral-naive and 73% with neurologic disease) with median baseline CD4+ cell counts, and plasma and CSF viral loads of 131/µL, 5.0 $\log_{10}$, and 3.5 $\log_{10}$ copies/mL, respectively. Of the factors studied, plasma HIV-1 RNA change ($R = .636$, $P = .002$), baseline CSF HIV-1 RNA level ($R = -.720$), $P < .0001$), months on HAART ($R = .643$, $P = .0001$), and the magnitude of the difference between the viral load in the plasma and CSF compartments ($R = .509$, $P = .0001$) significantly correlated with a CSF virologic response. The degree of CSF HIV-1 RNA reduction was higher in naive subjects and patients taking more than 3 drugs with adequate blood-brain barrier penetration.

Drug Transporters

In 4 symposium presentations, the concept of drug transporters and their role in interpatient variability in antiretroviral drug response was summarized.

As discussed in this session, P-glycoproteins (P-gp) are adenosine triphosphate–dependent cellular efflux pumps that are encoded by the multidrug resistance 1 (MDR1) gene. P-gp and CYP3A isozyme are frequently expressed in the same tissue, most notably in intestinal enterocytes, hepatocytes, and proximal tubules, and may share the same substrates. P-gp also appears to be involved in the maintenance of the blood–brain and genital tract barriers. Numerous antiretrovirals are P-gp substrates, including the protease inhibitors. Several are also P-gp inhibitors. Of the drugs related to AIDS therapy, indinavir, nelfinavir, saquinavir, and amprenavir are substrates of P-gp. Nelfinavir, saquinavir, ritonavir, clarithromycin, and itraconazole are among the many inhibitors of P-gp, while rifampin and constituents of St. John's wort are P-gp inducers. Because P-gp is both responsible, in part, for oral bioavailability and maintenance of the blood-brain barrier, P-gp and P-gp inhibitors/inducers could affect drug disposition by altering oral bioavailability and drug levels in compartments that would otherwise be relatively refractory to therapy.

As mentioned by several symposium speakers, there is genetic variability in the MDR1 gene. Silent polymorphisms in exon 26 are associated with differences in P-gp expression and therefore could affect drug disposition. In fact, in a separate presentation, Fellay and colleagues (Abstract 260) found that patients with homozygosity CC at P-gp codon 1145 (exon 26) had higher nelfinavir and efavirenz plasma levels than a TT allele. The effects on antiretroviral drug levels have previously been demonstrated in cell culture and animal models. For example, P-gp–overexpressing cells have 50%, 60% to 70%, and 70% decreased intracellular saquinavir, indinavir, and nelfinavir levels, respectively.

Several P-gp–specific third-generation inhibitors were mentioned, including GF120918 and LY335979, compounds with potent P-gp–inhibiting properties without significant effects on CYP3A. These diminish P-gp transport of saquinavir, nelfinavir, and indinavir and increase protease inhibitor central nervous system levels in an animal model and, therefore, could offer a means of increasing antiretroviral drug oral bioavailability and penetration into treatment-refractory body compartments such as the central nervous system and male genital tract.

Finally, in the last presentation of the session, Flexner and colleagues (Abstract

Table **4.** Pharmacokinetic Characteristics of Dual Protease Inhibitor, Single Protease Inhibitor Plus Pharmacokinetic Enhancer, or Protease Inhibitor/NNRTI Combinations

Abstract No.	Drug(s) and Dose(s)	Coadministered Drug(s) and Dose(s)	Interaction
739	Amprenavir/ritonavir 450 mg/200 mg bid or 600 mg/100 mg bid	With or without an NNRTI (efavirenz 600 mg qd or nevirapine 200 mg bid)	Amprenavir/ritonavir 450 mg/200 mg bid showed higher plasma amprenavir levels and less interpatient variability relative to 600 mg/100 mg bid with or without an NNRTI. Ritonavir 100 mg may not be adequate to compensate for the increased amprenavir clearance by nevirapine or efavirenz. The lowest amprenavir trough level with 450 mg/200 mg bid was approximately 3-fold higher than that attainable with standard amprenavir 1200 mg bid.
330	Nelfinavir 1200 mg bid	Saquinavir hard gel capsule (hgc) 1000 mg bid	Nelfinavir 1250 mg bid/saquinavir hgc 1000 mg bid achieved higher mean and median AUC and C_{max} for both agents relative to those for nelfinavir 750 mg tid/saquinavir hgc 600 mg tid combined with stavudine/lamivudine. Similar marker responses and tolerability were seen in the 2 study arms.
331	Saquinavir soft gel capsule (sgc) 1400 mg bid	Delavirdine 600 mg bid	Plasma saquinavir steady-state levels attained with saquinavir 1400 mg/delavirdine 600 mg bid were similar to those attained with standard saquinavir sgc tid dosing without delavirdine. Delavirdine levels were similar between the 2 saquinavir-containing arms with delavirdine dosed either tid (400 mg) or bid (600 mg).
336	Indinavir 1200 mg qd	Ritonavir 200 mg qd	In Merck 103/104 studies, indinavir/ritonavir 1200 mg/200 mg qd resulted in C_{max}, AUC_{24h}, and C_{24h} of 17.9 µM, 116 µMhr, and 156 nM. When added to stavudine/lamivudine, the resulting virologic and immunologic responses were comparable to those attained with historical standard dosed indinavir combination therapy responses.
738	Indinavir 400 mg bid or 400 mg bid or 600 mg bid or 800 mg bid	Ritonavir 100 mg bid or 400 mg bid or 100 mg bid or 100 mg bid	Indinavir C_{min} and C_{max}: 684 and 4624 ng/mL 788 and 4669 ng/mL 1094 and 6134 ng/mL 1532 and 8087 ng/mL Wide interpatient variability was seen with all the above regimens. The tolerability of the regimens increased in those containing lower indinavir doses. In general, adverse effects correlated with indinavir trough levels. C_{min} and C_{max} levels attained with the 400 mg/400 mg vs 400 mg/100 mg doses were not statistically different.
337	Indinavir 400 mg bid	Ritonavir 400 mg bid	Switching patients with plasma HIV-1 RNA suppression on standard indinavir 800 mg q8h-based therapy to an indinavir/ritonavir 400/400 mg bid regimen resulted in indinavir trough concentrations increasing in 26 of 27 subjects. After 3 weeks, indinavir median $C_{trough}/EC_{50,wildtype}$ increased from 2-fold with standard therapy to 15-fold with the indinavir/ritonavir combination ($P \leq .001$).
332	Amprenavir 600 mg bid or 1200 mg qd	Ritonavir 100 mg bid or 200 mg qd	In the APV20001 Study, subjects received open-label lamivudine/abacavir combined with either amprenavir 1200 mg bid or amprenavir/ritonavir 600 mg/100 mg bid or 1200 mg/200 mg qd. Respective steady state C_{min} were 0.26, 1.49, and 1.40 µg/mL, and C_{max} were similar (7.34, 5.39, and 7.75 µg/mL, respectively).
751	Indinavir 1000 mg tid or 1200 mg bid	Efavirenz 600 mg qd or 300 mg bid with or without abacavir	In a study of the population pharmacokinetic parameters of indinavir combined with efavirenz (ACTG 886 and 887 pharmacokinetic substudies of ACTG 368), the apparent oral clearance of indinavir was >1.5-fold higher than that with indinavir alone, although with high interpatient variability, possibly due to variable induction of indinavir metabolism by efavirenz.
753	Lopinavir 400 mg	Ritonavir 100 mg	The free fractions of lopinavir and ritonavir were similar in HIV-uninfected and HIV-infected subjects. The free fraction of ritonavir was similar in patients with normal and impaired hepatic function.

NNRTI indicates nonnucleoside reverse transcriptase inhibitor; AUC indicates area under the curve; C_{max} indicates maximum concentration; C_{min} indicates minimum concentration.

Table **5.** Pharmacokinetic Interactions with Antiretroviral Drugs

Abstract No.	Drug	Coadministered Drug(s)	Interaction
743	Saquinavir	Garlic supplements	Mean saquinavir AUC and 8-hour C_{min} and C_{max} were reduced by 51%, 49%, and 54%, respectively. These levels did not return to baseline after a 10-day washout period.
744, 745	Marijuana	Nelfinavir and indinavir	Smoked marijuana reduced the nelfinavir and indinavir 8-hour AUCs by 17% and 24%, respectively. No significant short-term marker of efficacy or safety effects were noted.
740	BMS-232632	Ritonavir	Relative to BMS-232632 200 mg or 400 mg qd, the addition of ritonavir 100 or 200 mg qd increased the mean BMS-232632 C_{min} from 9- to 18-fold and the AUC by 2- to 5-fold.
32	Rifampin	Efavirenz	Rifampin lowered efavirenz levels by >20%. The dose of efavirenz can be increased to 800 mg qd to compensate for this effect.
741	Rifabutin	Nelfinavir	No significant effect or reciprocal effect of these agents on the respective serum levels.
742	Rifabutin	Indinavir	No significant difference in enhanced rifabutin levels with treatment either staggered (separated by 4 hours) or with simultaneous indinavir coadministration. Relative to the standard rifabutin dose of 300 mg bid without indinavir, rifabutin 150 mg qd with indinavir 1000 mg tid resulted in rifabutin and 25-desacetyl rifabutin AUC increases of 60% and 125%, respectively.
579	Cyclosporine	Nevirapine or nelfinavir	Cyclosporine reduced nevirapine AUC by 35% and increased nelfinavir AUC by 100%, but by 6 months, AUCs returned to baseline. Reciprocally, there was a minimal reduction of cyclosporine levels by nevirapine, but a 50% reduction in the dose required to maintain the same AUC in the presence of nelfinavir.

AUC indicates area under the curve; C_{min} indicates minimum concentration; C_{max} indicates maximum concentration.

S4) outlined the findings that P-gp and even nonfunctional P-gp mutants appear to inhibit HIV replication, likely by interfering with gp160-mediated cell fusion and HIV budding. The proposed mechanism is a nonspecific interference of viral replication, since infected cell glycolipid-enriched membrane domains, or "lipid rafts," coincidentally localize both a significant proportion of P-gp and the region critical for viral budding. Therefore, the overall result of P-gp vis-à-vis antiretroviral drug disposition and viral replication in an HIV-infected cell may be a confluence of the seemingly contradictory effects: on the one hand, lowering intracellular antiretroviral concentrations, but also lessening the likelihood of a productive infection.

Therapeutic Drug Monitoring

The use of therapeutic drug monitoring as a means of improving clinical efficacy and predicting adverse drug effects was examined in a series of studies presented at the Conference. Selected studies are summarized in Table 6.

Clevenbergh and colleagues (Abstract 260B) reported data from the PharmAdapt Trial, a prospective multicenter randomized study that examined the utility of protease inhibitor therapeutic drug monitoring in treatment-experienced patients. This trial enrolled 256 patients who had at least 6 months of prior nRTI and/or NNRTI and/or protease inhibitor therapy and had baseline CD4+ cell counts of approximately 300/µL and plasma HIV-1 RNA levels of 4.3 $\log_{10}$ copies/mL. These subjects were then randomized into 2 study arms: a control (pK–) arm, where treatment was modified based on genotypic resistance testing, and a study arm (pK+), where treatment modification was based on genotypic testing as well as week-4 and -8 protease inhibitor trough levels. Optimal protease inhibitor trough concentrations were defined by levels greater than protein binding–adjusted IC_{50} for wild-type HIV-1. The opportunity of adding low pharmacokinetic-enhancing doses of ritonavir was offered and was used in 61% and 63% of control and study arm subjects, respectively. The study endpoints were plasma HIV-1 RNA responses at week 12.

For the week-4 pharmacokinetic assessment, suboptimal trough levels were seen in 8%/21% of indinavir, 0%/75% of saquinavir, 23%/0% of nelfinavir, 5%/12% of amprenavir, 0%/0% of lopinavir, and 69%/64% of ritonavir recipients in the control/study arms, respectively. At week 8, protease inhibitor dose modification was conducted in 10% and 22% of control and study subjects (P = .02). At week 12, the median $\log_{10}$ copies/mL plasma HIV-1 RNA decline and proportion below the level of

Table **6.** Selected Therapeutic Drug Monitoring Virologic Efficacy Trials

Study Name (Abstract No.)	Regimen(s)	Patient Population	Baseline Characteristics
PharmAdapt (260B)	PI (indinavir, saquinavir, nelfinavir, amprenavir, lopinavir, or ritonavir) with or without low-dose ritonavir (pharmacokinetic enhancement) plus nRTIs	256 antiretroviral-experienced (>6 months of prior therapy) patients	PVL: 4.3 $\log_{10}$ copies/mL CD4+ cell count: 300/μL
HIV-NAT 005 (730)	Zidovudine/lamivudine plus indinavir 800 mg tid or indinavir 800 mg/ritonavir 100 mg bid	19 Thai HIV-seropositive patients derived from the larger HIV-NAT 005 trial	PVL: 4.0 $\log_{10}$ copies/mL CD4+ cell count: 168/μL (median values)
M98-985 Study (337 and 523)	Indinavir 400 mg/ritonavir 400 mg or 300 mg bid plus current or switched nRTIs	37 patients with detectable viremia on standard indinavir/2-nRTI therapy	Indinavir experience: 32.1 months PVL: 3.3 $\log_{10}$ copies/mL CD4+ cell count: 325/μL (median values)

PI indicates protease inhibitor; nRTI indicates nucleoside reverse transcriptase inhibitor; PVL indicates plasma viral load; TDM indicates therapeutic drug monitoring; ITT indicates intent-to-treat; AUC indicates area under the curve; OT indicates on-treatment.

detection were comparable in the 2 groups: 2.61 versus 2.32 (P = .3) and 50% and 43% (P = .38), respectively). Neither the 4- or 8-week trough levels were predictive of the week-12 response (ITT analysis). The plasma viral load and number of protease inhibitor and NNRTI mutations at baseline were predictors of treatment response. Adverse events were equivalent in each group. The lack of difference between the study arms may have been related to a number of factors, including the chosen optimal trough concentration (>$IC_{50wild\text{-}type}$), the clinician's adherence to the genotypic/pharmacokinetic recommendations, patient adherence, and the prevalent use of ritonavir enhancement in both study arms.

In contrast, the utility of protease inhibitor plasma trough level monitoring in increasing virologic efficacy was demonstrated in several studies, including the M98-985 Study presented by Hsu and colleagues (Abstract 337). This was a trial of 37 patients with detectable viremia on indinavir–dual nRTI therapy and intensified to open-label indinavir/ritonavir/nRTI combination therapy. The investigators hypothesized that the resulting increased C_{min} would result in increased antiviral potency. The ritonavir dose was escalated to a final regimen of indinavir 400 mg/ritonavir 400 or 300 mg twice daily with current or switched nRTIs at week 3. At study entry, patients had a median of 32.1 months of indinavir experience and plasma HIV-1 RNA levels and CD4+ cell levels of 3.3 $\log_{10}$ copies/mL and 325/μL, respectively. With the indinavir/ritonavir combination, indinavir trough levels increased from 0.15 to 0.54 μg/mL (+272%) while AUC increased by 11% and C_{max} decreased by 51%. The median indinavir $C_{min}/EC_{50,wild\text{-}type}$ increased from 2-fold at baseline to 15-fold with indinavir/ritonavir. In a 48-week on-treatment analysis of patients with week-3 indinavir C_{min} greater than the median trough level (0.792 μg/mL), 88% of these subjects reduced their plasma HIV-1 RNA level below 400 copies/mL compared with 29% with indinavir trough levels less than or equal to the median 0.792 μg/mL week-3 level.

Kempf and colleagues (Abstract 523) further analyzed the data from the M98-985 Study to demonstrate that the virologic response to intensification with indinavir/ritonavir 400/400 mg twice daily was highly correlated with the virtual inhibitory quotient (VIQ). The VIQ is defined as the observed C_{min}/(virtual phenotype × serum-adjusted EC_{50} for wild-type HIV). The median indinavir VIQ was 8 (range, 0.5–85). At week 48, patients with indinavir VIQ of 2 or higher had greater virologic efficacy, with 80% response compared to 0% in those with indinavir VIQ less than 2 (P < .001). Using the indinavir virtual phenotype, 71% of patients had virologic response at 48 weeks, with less than 6-fold decrease in susceptibility compared to 43% with greater than 6-fold change. With intermediate (6- to 11-fold) increases in indinavir resistance, the virtual phenotype was not as effective as VIQ in predicting response subsequent to week 3. Responses were not correlated with the nRTI genotypic susceptibility score or the baseline HIV-1 RNA level.

Study Design	Study Endpoint(s)	Findings/Comments
Randomized comparison of PI TDM (indinavir plasma trough levels) and genotypic testing at weeks 4 and 8 (study arm) with genotypic testing alone (control arm).	Week-12 virologic response	PI trough levels at weeks 4 and 8 were not predictive of week-12 virologic efficacy (ITT analysis). PVL decreases in control and study arms (2.61 vs 2.32 $\log_{10}$ copies/mL, respectively; *P* = .3) and percent of patients with PVL below the level of detection (50% vs 43%, respectively; *P* = .38) were comparable. This may have been due to the frequent use of ritonavir pharmacokinetic enhancement or to nonadherence on the part of the clinicians or patients.
Open-label randomized correlation of indinavir pharmacokinetic parameters and virologic efficacy/safety. Breakpoints derived from receiver operating characteristic curves.	Week-24 virologic response and nephrotoxicity	Virologic failures (>50 copies/mL) were significantly more frequent in patients with indinavir C_{min}<0.10 mg/L (*P* = .025). The indinavir AUC correlated with nephrotoxicity (*P* = .04).
Intensification to open-label indinavir/ritonavir and correlation of indinavir pharmacokinetic parameters to virologic response.	Week-48 virologic response	88% of patients with week-3 indinavir trough levels > median trough level (0.792 µg/mL) had PVL <400 copies/mL vs 29% with trough levels ≤0.792 µg/mL (OT analysis). Patients with an indinavir virtual inhibitory quotient (VIQ) ≥2 had greater virologic efficacy than subjects with VIQ <2 (*P* < .001). VIQ was a better predictor of subsequent virologic response than a virtual phenotype, especially with intermediate increases (6- to 11-fold) in indinavir resistance.

In patients selected from the HIV-NAT 005 trial, the relationships between indinavir pharmacokinetic parameters and virologic efficacy and nephrotoxicity were examined (Burger et al, Abstract 730). In this trial, 19 Thai patients were randomized to zidovudine/lamivudine with indinavir 800 mg 3 times a day or indinavir/ritonavir 800/100 mg every 8 hours. Compared to a reference population of white patients from the Netherlands, indinavir AUC and C_{min} values were similar, although there was a delayed absorption phase with lower C_{max} values in the Thai patients. Virologic failures, defined by plasma HIV-1 RNA levels above 50 copies/mL at week 24, were significantly more frequent in patients with C_{min} less than 0.10 mg/mL (P = .025). AUC was significantly associated with nephrotoxicity (flank pain, hematuria, or an increase in serum creatinine >25%) (P = .04).

In a study examining the relationship between indinavir pharmacokinetic parameters and CD4+ cell response, Anderson and colleagues (Abstract 731) found a significant association between increased CD4+ cell counts and indinavir C_{max} independent of other covariates. In this study, antiretroviral-naive subject were randomized to either standard or concentration-targeted doses of indinavir/zidovudine/lamivudine. To elucidate pharmacokinetic parameters associated with CD4+ cell response, marker levels were assessed monthly or bimonthly and drug pharmacokinetic studies were done at weeks 2, 28, and 56. Median CD4+ cell count increases were 107, 174, and 245/µL at weeks 28, 56, and 80, respectively. In general, these values significantly correlated with indinavir C_{max} (P = .004, P = .01, and P = .08, respectively). The median indinavir C_{max} was 7 µg/mL. Subjects with values greater than this level had median CD4+ cell counts increases of 331/µL versus 175/µL in those individuals with C_{max} below 7 µg/mL (P = .006).

Conclusion

The 8th Conference on Retroviruses and Opportunistic Infections proved itself again to be the premier meeting devoted to bringing the latest information on pathogenesis and treatment together in 1 forum. Although no single breakthrough can be viewed as dominating the Conference, the totality of incrementally important new information was impressive and accurately portrayed the current status of the field. Further, although conservative approaches to initiating treatment related to the complications of currently available therapies may be dampening enthusiasm for antiretroviral therapy, one should be cautiously optimistic about the future of drug development. Simpler, less toxic, more potent therapies are a realistic goal and thus the pendulum can be expected to swing again in future years.

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