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Highlights of the 11th Conference on Retroviruses and Opportunistic Infections

The International AIDS Society–USA

About This Issue

This first issue of the 12th volume of *Topics in HIV Medicine* provides our annual review of selected new data presented at the 11th Conference on Retroviruses and Opportunistic Infections. The conference was held in San Francisco, California, between February 8 and 11, 2004.

Highlights of developments and new insights in basic science, including those around cellular cofactors that influence viral replication, are reviewed by Mario Stevenson, PhD. Magdalena E. Sobieszczyk, MD, Eoin P.G. Coakley, MD, Timothy J. Wilkin, MD, MPH, and Scott M. Hammer, MD, provide a summary of the new data around antiretroviral therapy that was presented at the conference. New research on investigational drugs, treatment strategies for antiretroviral naive and experienced patients, HIV resistance, prevention of mother-to-child transmission, and more are described. Finally, Judith S. Currier, MD, and Diane V. Havlir, MD, summarize the results of work around the characteristics and management of metabolic complications of antiretroviral therapy, new research on the opportunistic complications and coinfections associated with HIV infection, and issues that arise in pregnancy.

These articles are available on www.iasusa.org, and information on the 11th Conference on Retroviruses and Opportunistic Infections can be found at www.retroconference.org.

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Highlights of the 11th Conference on Retroviruses and Opportunistic Infections

Announcements

Developments in Basic Science Research

Mario Stevenson, PhD

As with last year's meeting, perhaps the greatest emphasis in the basic science categories was in the area of cellular cofactors that influence HIV-1 replication either positively or negatively. A number of presentations provided detailed insight into the mechanism by which APOBEC 3G, the cellular target of Vif, effects its antiviral activity. The surprising thing is that this antiviral activity is not restricted to primate lentiviruses but is active against retroviruses and even hepatitis viruses. In the area of positive-acting cellular cofactors, the emphasis was on those cellular proteins that facilitate egress of the virus from the infected cell. It is now apparent that viruses such as HIV-1 can bud into cytoplasmic vesicles in order to establish a unique intracellular reservoir. How viruses move between cells was also the focus of several presentations at the meeting, and there were further surprises about the mechanism by which HIV-1 may establish a latent infection.

Cellular Cofactors That Oppose Viral Replication

When considering mechanisms of host defense against viruses such as HIV-1, one traditionally thinks of the humoral and cellular arms of the immune response. Over the past several years, it has become increasingly apparent that in addition to the immune response, cellular factors exist within cells that counteract HIV-1 replication at various levels. The most dramatic example of a cellular factor that acts as an antiviral defense is the cellular protein APOBEC 3G, which was identified approximately 1to1.5 years ago as the cellular target for the HIV-1 Vif protein (Sheehy et al, *Nature,* 2002). Vif is a viral accessory protein that is essential for the replication of primate lentiviruses in primary cells, and viruses lacking Vif are made in a noninfectious form. Once Sheehy and colleagues identified the cellular target of Vif, a number of groups went on to demonstrate the mechanism by which viral replication is restricted in the absence of Vif (reviewed in Harris et al, *Nat Immunol,* 2003). Several presentations (Abstracts 63, 101, 103, 351) presented evidence that APOBEC 3G induces extensive deamination of deoxycytidine (dC) to deoxyuridine (dU) on minus-strand viral complementary DNA (cDNA) during reverse-transcription. This could negate viral replication by interfering with synthesis of the plus-strand cDNA. In addition, the cDNA could be targeted for destruction by, for example, the uracil DNA glycosolase-dependent pathway. An analogy between this process and the action of another deaminase known as activation-induced cytidine deaminase (AID, which is required for antibody gene diversification) was highlighted in the plenary presentation (Abstract 15). In order to protect themselves from APOBEC 3G, primate lentiviruses have evolved *vif* genes. A number of presentations focused on the mechanism by which Vif inhibits the action of APOBEC 3G (Abstracts 62, 103, 102). The consensus is that in order to induce deamination of minus-strand cDNA during reverse-transcription, APOBEC 3G must be incorporated into viral particles so that it can be present at the site of reverse-transcription after viral entry. Earlier studies in the field demonstrated that the cell that manufactures virions dictates the block to viral replication. Presentations at the conference indicated that in the presence of *vif,* the amount of APOBEC 3G that is incorporated into viral particles is reduced; further, in cells expressing Vif, the stability of APOBEC 3G is greatly reduced. Inhibitors of protease function increased APOBEC 3G stability, suggesting that Vif is somehow promoting degradation of APOBEC 3G in the proteasome. Proteins targeted for proteasome destruction are often ubiquitinated. Presentation 62 presented evidence that Vif directly interacts with E3 ubiquitin ligase, and that this results in mutual destruction of Vif and APOBEC 3G in the proteasome. Although progress in this area is significant, important questions remain. For example, the mechanism by which APOBEC 3G is incorporated into viral particles is not clear. In addition, if interaction between Vif and APOBEC 3G represents a future target for antiretroviral intervention, then it will be important to determine whether APOBEC 3G function is essential to the survival of the cell and to the host. CCR5 is an attractive target for therapeutic agents because individuals lacking functional CCR5 (homozygous Δ-32 deletion) are otherwise immunologically competent. Theoretically, small molecules that prevent interaction of Vif with APOBEC 3G would break down the viruses' defense against APOBEC 3G's antiviral activity.

With the exception of equine infectious anemia virus (EIAV), all primate and nonprimate lentiviruses have a *vif* gene. Therefore, APOBEC 3G or proteins of the same family may exert activity against a variety of lentiviruses. However, one study presented at the conference (Abstract 101) indicated that APOBEC 3G has the ability to inhibit very unrelated viruses. This is exemplified by the demonstration that hepatitis B viral replication is markedly impaired in cells that overexpress APOBEC 3G. It is possible that the levels of APOBEC 3G required to inhibit hepatitis B viral replication are not normally present in cellular reservoirs of hepatitis B viral replication, and that APOBEC 3G under physiologic conditions does not impact hepatitis B viral replication. However, one possibility is that proteins such as APOBEC 3G are regulated by, for example, the interferon response—and this may provide fundamental insight into the mechanism of innate host immunity against viruses. The fact that HIV-1 is a zoonosis was also made apparent by the demonstrations (Abstracts 103, 352, 353) that the species-specific activity of APOBEC 3G is governed by very specific genetic determinants. Thus, human

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APOBEC 3G is efficiently targeted for destruction by HIV-1 Vif, and APOBEC 3G from the African green monkey is not affected by HIV-1 Vif. Exchange of a single amino acid in human APOBEC 3G to the same residue as that in African green monkey APOBEC 3G allows it to be targeted by both HIV-1 and simian immunodeficiency virus (SIV) Vif. This graphically illustrates the fact that cellular defenses that restrict transmission of lentiviruses from monkeys to man can be overcome by subtle polymorphisms within genes such as *vif*.

Although APOBEC 3G acts at the level of reverse-transcription to block virus infection, there are additional cellular defenses that block infection before reverse-transcription, and these appear to target the incoming Gag protein (reviewed in Bieniasz, *Trends Microbiol,* 2003). The existence of cellular restrictions was identified more than 3 decades ago, when mice were found to carry genetic traits that control susceptibility to leukemia induced by the Friend-strain of murine leukemia virus (MLV)—a phenomenon dubbed "Friend virus susceptibility" (Fv). More recently, similar restrictions termed lentivirus susceptibility-1 (Lv1) and restriction factor-1 (REF1) were shown to inhibit a range of retroviruses, including HIV-1. These restrictions appear to target the Gag protein since the block to infection can be saturated by overexpression of capsid proteins from incoming virions. In the case of Lv1, this activity restricts infection of nonhuman primate cells by viruses such as HIV, SIV, and EIAV; REF1, on the other hand, is expressed by human cells and prevents infection by retroviruses such as MLV. Studies presented at the meeting (Abstracts 104, 356, 357) presented evidence that Cyclophilin A confers differential sensitivity to Lv1 and REF1 restrictions. Cyclophilin A is a host cell protein previously shown to be important for efficient uncoating of the viral capsid following viral entry. This rule has now been revised. Owl monkey cells are resistant to HIV-1 infection because of the presence of Lv1. However, if the interaction of Cyclophilin A with capsid is blocked using cyclosporine A, HIV-1 infectivity is increased by 2 logs. Conversely, preventing Cyclophilin A-capsid interactions in human cells restricts HIV-1. How this differential effect is manifested will probably become clearer once the actual proteins that constitute Lv1 and REF1 are identified, and should further provide novel drug targets over therapeutic intervention.

Presentation 105 described the identity of a factor called ZAP that inhibits replication of retroviruses such as MLV, as well as alphaviruses including Sindbis and Semliki Forest. ZAP was not active against HIV-1. In contrast to the previously discussed restriction factors, ZAP does not prevent viral entry and integration but appears to destabilize or inhibit nuclear export of retroviral messenger RNAs (mRNAs). ZAP contains a zinc finger motif that interacts with MLV RNA near the 3'-end. ZAP also contains a protein destabilization motif. It is likely that APOBEC 3G, Lv1, REF1, and ZAP are the first of a number of yet-to-be-identified restriction factors targeted to primate and nonprimate lentiviruses. This is likely to be a fruitful area of research for the next several years.

Positive Cellular Cofactors

Viruses such as HIV-1, despite a limited genetic repertoire, still have to carry out a number of functions. Therefore, it is not surprising that these viruses abscond with cellular proteins and cellular pathways in order to complete various steps in viral replication. Perhaps the best illustration of this is receptor and coreceptor molecules required for viral entry. The transacting factor Rev relies upon the nuclear export factor Crm-1 for its proper functioning, and the transacting protein Tat is simply a recruitment factor for the cellular protein Cyclin T1 that promotes transcriptional activation from the long-terminal repeat (LTR). New cofactors important for detachment of assembling viral particles from the plasma membrane were presented at the conference (Abstracts 6, 64, 65). During HIV-1 assembly, the viral Gag protein binds genomic viral RNA and then interacts with the plasma membrane to assemble into enveloped particles that bud from the infected cell (Pornillos et al, *Trends Cell Biol,* 2002). These enveloped particles must detach from the plasma membrane by a fission event that severs the membrane of the assembling virion from the cellular membrane. Since expression of Gag protein in the absence of other viral proteins is sufficient to recapitulate virus budding and detachment, there must be cellular proteins that interact with Gag that promote this fission event. The first such cellular protein that was recognized to be involved in this step was tumor-suppressed susceptibility gene 101 (Tsg-101). It was identified in a yeast 2 hybrid genetic screen on the basis of its ability to bind to a motif in the p6 region of Gag known as the late domain. This domain is so named because mutations within it lead to a defect at a late step in viral replication (ie, virion detachment). Tsg-101 is a component of the Class E vacuolar sorting (Vps) machinery. As discussed at the meeting, Tsg-101 is one of a family of Class E Vps proteins that participate in the assembly and release of viral particles. Furthermore, the Vps proteins are important for the release of other pathogenic human viruses like Ebola virus and human T-cell leukemia virus Type 1 (HTLV-1). Considering the normal function of Tsg-101, the reason viruses such as HIV-1 have adopted it for their own uses becomes apparent. Tsg-101 normally functions in the cellular vacuolar protein-sorting pathway by selecting cargo for incorporation into vesicles that bud into endosomes, so as to create multivesicular bodies (MVBs). The formation of MVBs, which involves budding of vesicles away from the cytoplasm, contrasts the formation of, for example, endocytic vesicles, which bud into the cytoplasm. Since virus budding to the exterior of the cell parallels vesicular budding into the MVBs, it is expected that these processes depend upon the same cellular machinery. Indeed, more than a decade ago, it was demonstrated that in macrophages, HIV-1 could assemble into cytoplasmic vesicles, and more recently, these vesicles were identified as MVBs (Raposo et al, *Traffic,* 2002). Upon first demonstration, this process was considered an experimental curiosity. However, there is an increasing suspicion that viral particles that enter MVBs in cells such as macrophages may constitute a unique cellular reservoir for viral persistence. Data presented at the conference (Abstract 46) indicated that all the viruses released from infected macrophages originate from MVBs, and other data (Abstract 65) examined how

the processes of plasma membrane assembly at the MVB may be regulated in different cell types. In that study, the ability of Gag to localize to the plasma membrane required interaction with the plasma membrane lipid phosphatidylinositol-(4,5)-biphosphate (PIP_2). Depletion of PIP2 resulted in Gag being targeted to the MVB. One possibility is that in macrophages, where virus budding is predominant, the MVB, PIP_2 may be rate-limiting. These studies illustrate the existence of 2 potential routes for Gag targeting that may define how viruses are sequestered and ultimately transmitted to neighboring cells. MVBs typically fuse with the plasma membrane and release vesicular contents (including viruses) at points of contact with neighboring T cells, and hence may represent an efficient mechanism for cell-to-cell transfer of viral particles. One important question regarding the assembly of HIV-1 virions into the MVB is the fate of those particles. MVBs often undergo acidification that would be predicted to rapidly inactivate vesicularized virions. At present, it is unclear if viruses sequestered within MVBs retain infectivity or if there are specialized MVBs that do not undergo acidification and can retain vesicularized viruses over extended periods. These questions are relevant to the issue of viral persistence in macrophage reservoirs.

A distinguishing feature between lentiviruses such as HIV-1 and oncoretroviruses such as MLV is the former's ability to infect nonmitotic cells. The current consensus is that nucleophilic proteins associated with the incoming viral reverse-transcription complex allow the complex to traverse the nuclear envelope in order to promote contact of viral cDNA with host cell chromatin. Integrase has been suggested as a potential nuclear import factor that allows infection of nondividing cells. Integrase catalyzes the insertion of the viral cDNA into cellular DNA of the infected host cell. Lens epithelium-derived growth factor, p75 (LEDGF) has been identified as a cellular protein that interacts with integrase. Two studies (Abstracts 68, 337B) presented evidence that LEDGF dictates nuclear localization of integrase. Therefore cellular proteins such as LEDGF, through their interaction with integrase, may dictate nuclear import of the viral cDNA. In agreement with this model, both studies presented evidence that mutations in LEDGF that prevent association with integrase result in a redistribution of integrase from the nucleus to the cytoplasm. Both studies then used an RNA-interference strategy to inhibit the expression of LEDGF in cells in order to gauge the effect on viral replication. One study's results (Abstract 337B) found that depletion of LEDGF did not affect viral replication. The other study's results (Abstract 68) found that inhibition of LEDGF expression by RNA-interference blocked viral replication by preventing association of viral cDNA with chromatin, but not nuclear import. The reasons for these differences are unclear, and further studies are required in order to determine whether LEDGF is a cofactor for HIV-1 replication.

Although there is a general consensus that lentiviruses such as HIV-1 infect nondividing cells because they contain nucleophilic functions that promote nuclear entry of the reverse-transcription complex, there is no agreement on the viral factors that promote nuclear uptake of the reverse-transcription complex. One study (Abstract 67) presented surprising findings that MLV/HIV-1 chimeric viruses in which the capsid protein is exchanged altered the viruses' ability to infect nondividing cells. However, there is no strong evidence that the capsid protein of HIV-1 is actually retained within reverse-transcription complexes as it translocates to the host-cell nucleus. Therefore, the authors suggest that capsid acts as a barrier to nuclear import by masking receptors on the reverse-transcription complex that interact with nucleophilic viral or cellular factors. In the case of MLV, which cannot infect nondividing cells, the association of capsid with the reverse-transcription complex would prevent this virus's ability to access the nondividing nucleus. In the case of HIV-1, since capsid is not retained, binding sites on the reverse-transcription complex for nucleophilic factors are exposed for binding nucleophilic factors that promote HIV-1 infection of nondividing cells. The actual viral and cellular factors that mediate the import process itself await validation.

Viral Replication and Transmission

Infectious virion particles serve as conduits for the transmission of genomic viral RNA from the infected cell to new substrate cells. The general consensus is that virions are released into the extracellular space and then randomly encounter new target cells. Studies presented at the conference (Abstracts 44, 45, 46) support the notion that viruses such as HIV-1 may have evolved the ability to exploit the antigen-presenting properties of macrophages and dendritic cells in order to promote efficient cell-to-cell viral dissemination. As discussed earlier, viruses assemble into MVBs of macrophages and are released by exocytosis onto neighboring cells. In dendritic cells, evidence was presented (Abstract 44) that HIV-1 virions are internalized into a late endosomal compartment, as evidenced by expression of tetraspanins such as CD81, a marker for the MVB. This compartment into which virions are internalized lacks early and late endosomal markers, suggesting that viruses may not be rapidly inactivated by acidification. Upon contact with T cells, the compartment harboring virions appeared to localize at the synapse between the dendritic cell and the T cell. Such a synapse would provide a favorable environment for the efficient transfer of internalized particles to target T cells. In addition, since the synapse also involves the display of costimulatory molecules to the T cell, it is likely that T cells involved in the synapse would be brought into a state of readiness to allow viral infection and replication. Continuing on with this theme, abstract 45 presented evidence that synapses formed between infected and uninfected T cells promote recruitment of CD4, CXCR4, and LFA-1 on the target cell, as well as envelope and Gag proteins on the infected cell, and coordinate transfer of viral proteins into the target cell. Receptor and coreceptor recruitment on the target cell were mediated through Actin, suggesting that the effector cell transmits signals, perhaps through envelope engagement of CXCR4 on the target cell, that promote further recruitment of coreceptor and costimulatory molecules that favor viral transmission. Studies of this kind have

important implications regarding the mechanism of viral dissemination and the ability of the immune response to contain it. Cell-free viral particles are rapidly cleared by the reticuloendothelial system of the host and are also subject to neutralization by circulating antibody. These forces may be less able to prevent viral dissemination in the context of a virologic synapse.

The establishment of a reservoir of latently infected cells is considered the single biggest obstacle to HIV-1 eradication by potent antiretroviral therapy. However, the mechanism through which latently infected cells are established is still unclear. Since a number of studies have indicated that truly quiescent (G_0) T cells are refractory to infection, it is generally agreed that latency is established when a cycling cell is infected and then returns to quiescence before viral cytopathic effects or immunologic clearance mechanisms destroy the infected cell. A study presented at the conference (Abstract 123LB) suggests that HIV-1 can infect and integrate within quiescent lymphocytes. This observation is at odds with a number of published studies that suggest the viral life cycle is blocked before integration in quiescent cells. The difference in this study is that the investigators used spin-inoculation to increase the efficiency of infection. One possibility is that the process of spin-inoculation provides a subtle stimulus that brings the cells out of quiescence. Therefore, this observation needs confirmation, but it nevertheless suggests that infected quiescent lymphocytes could potentially represent the immediate precursor to the latently infected T cell.

In the same session, data were presented suggesting that the chronic activation state seen in pathogenic HIV-1 and SIV infections may be partly due to the infection and destruction of cells that suppress T-cell activation. In contrast to pathogenic HIV-1 and SIV infections, SIV in its natural host (for example, the African green monkey) does not cause disease, and this has been correlated with a lack of immune hyperactivation. CD4+ and CD25+ T cells (also known as Treg cells) have the capacity to suppress T-cell activation. In Abstract 124LB, Treg cells were shown to be highly susceptible to HIV-1 infection. This suggests that the disruption of the T-cell regulatory system by HIV-1 infection may remove the controls to hyperactivation of conventional T cells, thereby contributing to the chronic activation state that is characteristic of AIDS progression.

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Conference Abstracts cited in text can be found at www.retroconference.org.

Additional Suggested Reading

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Advances in Antiretroviral Therapy

Magdalena E. Sobieszczyk, MD, Eoin P.G. Coakley, MD, Timothy J. Wilkin, MD, MPH, and Scott M. Hammer, MD

Antiretroviral therapy was a focus of many of the studies reported at the 11th CROI. This year, data on new drugs, refinements in the management of treatment-naive and treatment-experienced persons, the impact of drug resistance (particularly following exposure to a single dose of nevirapine), and the growing experience with antiretrovirals in the developing world were the dominant themes. This review summarizes new information relevant to clinicians and clinical researchers.

Investigational Antiretroviral Drugs

Results of select studies of investigational antiretroviral drugs are summarized in Table 1.

Entry Inhibitors

CCR5 Antagonists. SCH D is a CCR5 receptor antagonist that has supplanted SCH C in the development process. SCH D proved more potent in vitro than SCH C and also has a longer half-life, better absorption, and higher bioavailability, based on rat and monkey studies. Schurmann and colleagues (Abstract 140LB) presented results of a study evaluating SCH D monotherapy in chronically HIV-infected subjects. A total of 48 subjects with baseline plasma HIV-1 RNA levels between 5,000 copies/mL and 200,000 copies/mL and CD4+ counts greater than 250 cells/µL, who were off antiretroviral therapy for 8 weeks, were randomized to receive 10 mg of SCH D twice-daily (bid); 25 mg of SCH D bid; 50 mg of SCH D bid, or placebo for 14 days. Mean change in plasma HIV-1 RNA levels from baseline was -1.08 $\log_{10}$ copies/mL, -1.56 $\log_{10}$ copies/mL, and -1.62 $\log_{10}$ copies/mL in the 10 mg-, 25 mg-, and 50 mg-dose groups, respectively. All doses were well tolerated. One patient with plasma HIV-1 RNA reduction of greater than 1.5 $\log_{10}$ copies/mL had evidence of a transient switch to X4 virus after treatment.

GW873140 is a novel, orally bioavailable CCR5 receptor antagonist. Demarest and colleagues (Abstract 139) presented data from a double-blind, randomized, placebo-controlled, single- and multiple-dose escalation study conducted in 70 non-HIV infected volunteers. Preliminary data indicated that this compound was well tolerated with no serious adverse events. Most of the side effects were gastrointestinal; 4 patients who received multiple doses had lipase increases. Ingesting the drug with food increased the area under the concentration curve (AUC) and C_{max} by means of 1.7- and 2.2-fold, respectively. CCR5 receptor occupancy depended on the drug dose and the sampling time; baseline binding analyses showed 0% receptor occupancy, 93% to 99% dose-dependent occupancy at 2 hours, and over 97% receptor occupancy at 12 hours, at all doses. Receptor-binding analyses 24 hours after a single dose showed median receptor occupancy ranging from 68% to 88%, despite compound concentrations below or near assay limits. At 2 and 12 hours after multiple dosing with GW873140, the CCR5 occupancy was greater than 97%. These findings suggest a long half-life for the compound–receptor binding, with once daily (qd) or bid dosing schedules. Studies of GW873140 in HIV-infected individuals are planned.

Attachment Inhibitors. BMS-488043 is an orally available HIV entry inhibitor, which binds specifically to gp120 and interrupts the attachment of the viral envelope to the CD4 receptor. Lin and colleagues (Abstract 534) demonstrated that BMS-488043 binds reversibly to gp120 with a 1:1 stoichiometry, and that its activity is coreceptor independent. Data from a limited number of isolates indicate that this agent is effective against both X4 and R5 laboratory strains, and has good in vitro potency against subtype B clinical isolates (median 50% effective concentration [EC_{50}] of 37 nM). BMS-488043 has a long half-life and a good safety profile in non-infected volunteers in single-dose and in multiple-dose studies (Abstract 535). C_{max} and AUC values appeared to be dose-related for those of 200 mg to 800 mg, with no significant increase in exposure seen at higher doses. Exposures were generally higher with a high-fat meal than with a light meal. The authors concluded that a dose of 800 mg bid is expected to provide adequate plasma concentrations for suppression of subtype-B HIV-1 isolates.

Hanna and colleagues (Abstract 141) compared the antiviral activity of BMS-488043 monotherapy with placebo over 8 days. HIV-1-infected patients with plasma HIV-1 RNA levels between 5,000 and 500,000 copies/mL and CD4+ counts above 250 cells/µL, who were treatment naive or off antiretrovirals for more than 16 weeks, received 800 mg (n = 12) or 1800 mg (n = 12), bid. The mean baseline CD4+ count was 395 cells/µL and plasma HIV-1 RNA level was 4.61 $\log_{10}$ copies/mL. Approximately 50% of subjects were treatment naive. On day 8, the mean change in plasma HIV-1 RNA level from baseline was -0.72 $\log_{10}$ copies/mL and -0.96 $\log_{10}$ copies/mL for 800 mg and 1800 mg doses, respectively. The majority of patients had at least a 1-$\log_{10}$ decline in

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Table **1.** Summary of Selected Investigational Antiretroviral Drugs

Drug	Abstract(s)	Drug Class or Mechanism of Action	Development Stage	Results
D-D4FC	137	nRTI	Phase II studies in HIV-infected individuals	1.77 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA levels after 10 days of monotherapy[1]
SPD 754	138, 526, 527, 599	nRTI	Phase II studies in HIV-infected individuals. Long-term toxicity studies in animals	1.65 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA from baseline after 10 days of therapy with a 1200 mg dose. Comparable efficacy in patients with preexisting NAMs
SN1212/1461	532	nRTI	Preclinical	EC_{50}, 10-100 nM
Diarylpyrimidines (DAPYs) and Diaryltriazines (DATAs)	528	NNRTI	Preclinical	EC_{50}, 0.4-3.0 nM
678248 and 695634 (678248 prodrug)	529	NNRTI	Preclinical	IC_{50} 1.8 nM against wild-type, and IC_{50} 0.8-6.8 nM against reverse transcriptase mutants
SCH D	140LB	Entry Inhibitor (CCR5)	Phase II studies in HIV-infected subjects	1.08-1.62 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA levels after 14 days of monotherapy[2]
GW873140	139	Entry Inhibitor (CCR5)	Phase I study in HIV-seronegative subjects	Greater than 97% receptor binding 12 hours after dosing
AMD887	539	Entry Inhibitor (CCR5)	Preclinical	EC_{50}, 1-10 nM[5]
KRH-2731 Orally bioavailable	541	Entry Inhibitor (CXCR4)	Preclinical	EC_{50}, 1-4.2 nM
BMS-488043	141, 534, 535	Attachment Inhibitor	Phase II study in HIV-infected subjects	0.72-0.96 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA levels after 8 days of monotherapy[3]
PA-457	545	Gag processing inhibitor (inhibits processing of p24 capsid protein)	Preclinical	Inhibits Gag CA-SP1 cleavage site. Does not inhibit the P450 enzyme system (IC_{50}, >100 nM)
TMC114	533	Protease inhibitor	Phase IIa study in HIV-infected subjects	1.24-1.50 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA levels after 14 days as functional monotherapy[4]

[1]Participants were antiretroviral-naive; median baseline plasma HIV-1 RNA level was 4.2 $\log_{10}$ copies/mL. D-D4FC was administered as monotherapy in doses ranging from 50 mg to 200 mg. The greatest efficacy was seen at the 200 mg dose.

[2]Subjects had baseline plasma HIV-1 RNA levels between 5,000 copies/mL and 200,000 copies/mL and were off antiretroviral therapy for 8 weeks.

[3]Mean baseline plasma HIV-1 RNA level was 4.6 $\log_{10}$ copies/mL, and subjects were antiretroviral naive (50%) or off antiretrovirals for more than 16 weeks.

[4]Patients were receiving failing regimen and at baseline had 3 major protease inhibitor (PI) mutations. For patients with more than one PI mutation at baseline, the median drop in plasma HIV-1 RNA levels was 1.44 $\log_{10}$ copies/mL.

[5]When AMD887 was combined with AMD070 (a CXCR4 antagonist), viral replication was suppressed in peripheral blood mononuclear cells.

nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NAM, nRTI-associated resistance mutation; EC_{50}, 50% effective concentration; IC_{50}, 50% inhibitory concentration

plasma HIV-1 RNA level: 58% in the 800 mg group and 67% in the 1800 mg group. After 8 days of therapy, the mean increase in CD4+ count was 106 cells/µL in the 800 mg arm, 48 cells/µL in the 1800 mg arm, and 30 cells/µL in the placebo arm. These differences, however, were not statistically significant. Overall, the drug was well tolerated; fatigue was noted in 4 of 15 subjects and headaches in 2 of 15 in the 800 mg arm. This proof of concept study supports the further development of this novel class of attachment inhibitors that target gp120.

Monoclonal antibody to CD4. TNX-355 is a viral entry inhibitor, an IgG4 monoclonal antibody that targets domain 2 of the CD4 receptor. This specificity of binding allows for inhibition of post-binding viral entry and fusion without causing immunosuppression. Jacobson and colleagues (Abstract 536) presented results from a study of 21 HIV-1-infected individuals with plasma HIV-1 RNA levels greater than 5,000 copies/mL and CD4+ counts between 100 cells/µL and 500 cells/µL, who were randomized into 1 of 3 treatment arms: 10 mg/kg every 7 days for 10 weeks (n=9); 10 mg/kg on the first day followed by 6 mg/kg every 14 days for 6 doses (n=10); and 25 mg/kg every 14 days for 5 doses over 8 weeks (n=3). One subject was antiretroviral naive. The mean baseline CD4+ count and plasma HIV-1 RNA level were 332 cells/µL and 4.78 $\log_{10}$ copies/mL, respectively. Mean reductions in plasma HIV-1 RNA of 1.11 $\log_{10}$ copies/mL and 0.96 $\log_{10}$ copies/mL occurred by week 2 in the 2 highest doses (10 mg/kg and 25 mg/kg). At week 9 (final dosing), plasma HIV-1 RNA levels had returned to baseline; reduced susceptibility to TNX-355 was seen in 16 subjects. CD4+ counts rose transiently and the maximal median elevations above baseline in the 3 treatment groups were 257 cells/µL, 198 cells/µL, and 103 cells/µL. No CD4+ count depletion was noted. Complete and continuous CD4+ cell coating was observed for a minimum of 14 days after the final dose was administered in each study arm. Two subjects were withdrawn, 1 due to new onset seizure and 1 to a protocol violation (illicit drug use); other serious adverse events included recurrence of depression and transient acute renal failure. A phase II study of this agent in combination with optimized background therapy in antiretroviral-experienced patients is planned.

Protease Inhibitors

TMC114. Peeters and colleagues (Abstract 533) presented the results of a phase IIa, open label, randomized study of TMC114 coadministered with a boosting dose of ritonavir in protease inhibitor (PI)-experienced patients. Patients with no current AIDS defining illnesses, plasma HIV-1 RNA levels above 2000 copies/mL, previous treatment with 2 to 4 PIs for more than 2 months each, virologic failure of the current regimen, and no nonnucleoside reverse transcriptase inhibitor (NNRTI) use in the failing regimen were eligible for study participation. Fifty patients were randomized into 4 study arms: TMC114 300 mg/ritonavir 100 mg bid (n=13); TMC114 600 mg/ritonavir 100 mg bid (n=12); TMC114 900 mg/ritonavir 100 mg qd (n=13); or continuation of current therapy. Background nucleoside reverse transcriptase (nRTI) treatment was not changed. The median baseline plasma HIV-1 RNA level and CD4+ count were 4.26 $\log_{10}$ copies/mL and 305 cells/µL, respectively. At baseline, 16 of 35 patients had virus with phenotypic resistance to all PIs (atazanavir not tested); the median baseline number of major PI mutations in all groups was 3, and no significant genotypic and phenotypic differences for PIs were observed between groups. At day 14 of therapy, the median change in plasma HIV-1 RNA from baseline was -1.24 $\log_{10}$ copies/mL in the 300 mg/100 mg arm; -1.25 $\log_{10}$ copies/mL in the 900 mg/100 mg arm; and -1.50 log10 copies/mL in the 600 mg/100 mg arm. The median plasma HIV-1 RNA change from baseline to day 14 in the 900 mg/100 mg and 600 mg/100 mg study arms was significantly greater than in the control arm ($P<0.05$ and <0.001, respectively). There were no significant differences in antiviral response in subgroups divided according to baseline plasma HIV-1 RNA. For all treated subjects with more than one major PI mutation, the median plasma HIV-1 RNA change from baseline to day 14 was -1.44 $\log_{10}$ copies/mL (range -0.47 to -2.49 $\log_{10}$ copies/mL); this was statistically significant compared with the control arm ($P<0.05$). In patients with phenotypic resistance to lopinavir, the median plasma HIV-1 RNA decrease from baseline was 1.50 $\log_{10}$ across all treatment groups; patients with a baseline resistance to all PIs had a median plasma HIV-1 RNA decrease of 1.50 $\log_{10}$ copies/mL. A randomized phase IIb trial is under way to evaluate the optimal dose and schedule of TMC114/ritonavir in PI-experienced patients.

Reverse Transcriptase Inhibitors

D-D4FC. Murphy and colleagues (Abstract 137) presented preliminary results of a study evaluating D-D4FC (no generic name for this drug is yet available) monotherapy in antiretroviral-naive patients. D-D4FC is an nRTI that has in vitro activity against HIV-1 isolates resistant to zidovudine, lamivudine, and other nRTIs. It loses activity only in the presence of the Q151M resistance mutation or an amino acid insertion at position 69 of HIV-1 reverse transcriptase. Thirty subjects with CD4+ counts greater than 50 cells/µL and plasma HIV-1 RNA levels greater than 5,000 copies/mL were randomized to receive 50 mg, 100 mg, or 200 mg of D-D4FC (qd), or placebo for 8 days. At baseline, the median plasma HIV-1 RNA level and CD4+ count were 4.2 $\log_{10}$ copies/mL and 486 cells/µL, respectively. At day 6, the mean plasma HIV-1 RNA change was -1.2 $\log_{10}$ copies/mL in the 50 mg arm; -1.19 $\log_{10}$ copies/mL in the 100 mg arm; and –1.32 $\log_{10}$ copies/mL in the 200 mg arm. In the 200 mg arm, the mean plasma HIV-1 RNA change from baseline to day 10 was 1.77 $\log_{10}$ copies/mL. Small increases in CD4+ cell counts were observed during the treatment period but returned to pretreatment levels during the 1-month follow-up period. There was no evidence of selection of resistance mutations. All adverse events were mild to moderate and included cold symptoms, headaches, and fatigue; the incidences were similar in the treatment and placebo arms. Long-term toxicity studies were done in rats and dogs; bone marrow toxicity and enteropathy were seen

only in the former. A phase IIb study is currently recruiting patients and will evaluate the efficacy and safety of D-D4FC in treatment-experienced patients in whom previous nRTI-containing regimens had failed.

SN1212/1461. SN1212/1461 is a novel mutagenic deoxyribonucleoside analogue that can inhibit viral growth in tissue culture (Abstract 532). SN1461 is an oral prodrug of SN1212. This agent is not a chain terminator and has an unmodified sugar and thus is unlikely to be affected by lack of affinity of reverse transcriptase for a modified sugar or pyrophosphorolysis, the 2 major mechanisms of nRTI resistance. The EC_{50} of SN1212 is 10 nM to 100 nM. SN1212-treated virus had a more than 50% increase in mutation rate in reverse transcriptase and Env above controls; no SN1212 resistant HIV were isolated. At a dose of 320 µM, the agent did not result in mitochondrial toxicity. No toxicity was observed in dogs after administration of the prodrug in doses of up to 2g/kg.

SPD754. SPD754 is a deoxycytidine analogue that has shown antiviral activity in treatment-naive patients. At this meeting, new pharmacologic evaluation data in humans, resistance profile, and preclinical safety profile of the agent after prolonged administration to monkeys were presented. Bethel and colleagues (Abstract 138) examined the effect of lamivudine on SPD-754 phosphorylation. Twenty-one HIV-1 seronegative individuals received either SPD754 600 mg bid, lamivudine (qd), or both drugs for 4 days, followed by a 7-day washout period. Pharmacokinetic profile of SPD754, and lamivudine and lamivudine-TP, SPD754-triphosphate (TP) were determined in plasma and peripheral blood mononuclear cells (PBMCs). Although the study showed that plasma pharmacokinetics of SPD754 alone and in combination with lamivudine are the same, the intracellular concentration of phosphorylated SPD754 was reduced up to 6-fold in the presence of lamivudine or lamivudine metabolites. Lamivudine decreased the effect of SPD754 against M184V mutant HIV virus by at least 2- to 3-fold. In contrast, SPD754 had no effect on intracellular lamivudine-TP concentrations. The authors concluded that these findings would preclude the coadministration of lamivudine and SPD754 in the clinical setting. Additional data on the intracellular pharmacokinetics of SPD754-TP in PBMCs of HIV-infected patients were presented by Adams and colleagues (Abstract 599), who showed that the half-life of SPD754-TP in mononuclear cells was approximately 6 to 7 hours, and that intracellular concentrations of SPD754-TP showed some correlation with plasma concentrations. Collins and colleagues (Abstract 526) presented clinical resistance profile of SPD754 after 10 days of monotherapy in antiretroviral naive-patients. Sixty-four patients with CD4+ counts greater than 250 cells/µL and plasma HIV-1 RNA levels of 5,000 copies/mL to 1000,000 copies/mL were randomized to 1 of 6 dosage regimen or a placebo. Baseline genotyping was performed on samples from 56 patients, 4 patients had preexisting nRTI-associated resistance mutations (NAMs), 3 of them received the drug, and 1 received placebo. On day 10, the mean drop in plasma HIV-1 RNA levels was 1.18 $\log_{10}$ copies/mL for the 400 mg dose and 1.65 $\log_{10}$ copies/mL for the 1200 mg dose (Cahn et al, 2nd IAS Conference, 2003). On day 10, all 3 patients with the NAM achieved a drop in plasma HIV-1 RNA within 1 standard deviation of the mean change seen in plasma HIV-1 RNA in patients with the wild-type virus at baseline. Overall, no new NAMs emerged after 10 days of monotherapy with SPD754. The authors concluded that this agent warrants further investigation for the treatment of nRTI-resistant virus in combination with other agents. Similarly encouraging were the results of 52 weeks of treatment with SPD754 administered to cynomolgus monkeys, which revealed only minimal and reversible mucocutaneous hyperpigmentation, mild gastrointestinal effects, and minimal changes in red blood cell counts (Abstract 527).

Treatment of Antiretroviral-Naive Patients

Results of select studies in antiretroviral-naive patients are summarized in Table 2.

2NN Substudy

Van Leth and colleagues (Abstract 550) presented additional results from the 2NN trial that compared the antiviral activity of nevirapine, efavirenz, and the combination of nevirapine/efavirenz in the treatment-naive, HIV-infected patients. This substudy analyzed virologic efficacy of each regimen according to baseline CD4+ cell count and plasma HIV-1 RNA level. Patients were randomized to receive a backbone of stavudine/lamivudine with nevirapine qd, nevirapine bid, efavirenz qd, or nevirapine/efavirenz bid. Patients were divided into 3 groups based on their baseline CD4+ counts (< 25 cells/µL, 25 cells/µL to 199 cells/µL, or > 200 cells/µL) and 2 groups according to their baseline plasma HIV-1 RNA levels (< 100,000 copies/mL or > 100,000 copies/mL). Virologic failure was defined as never reaching plasma HIV-1 RNA levels below 400 copies/mL during follow-up, or rebounding to above 400 copies/mL. At week 48, patients with baseline CD4+ count less than 25 cells/µL had a statistically significantly higher risk of virologic failure than did patients with baseline CD4+ counts of at least 200 cells/µL ($P = 0.04$; hazard ratio [HR] = 1.50). Patients with a baseline plasma HIV-1 RNA above 100,000 copies/mL had a statistically higher risk of virologic failure ($P = 0.004$, HR = 1.48). The nevirapine-only groups were combined because there were no differences in outcome between these arms. In each CD4+ stratum, patients with baseline plasma HIV-1 RNA above 100,000 copies/mL had a higher risk of virologic failure, except in the CD4+ stratum with more than 200 cells/µL for nevirapine. There were no statistically significant differences between the nevirapine and efavirenz groups, and the authors suggested that, in patients with advanced disease, there is no convincing evidence that either efavirenz or nevirapine is favorable for first-line treatment.

FORTE Trial

The FORTE trial (Abstract 564), presented by Williams and colleagues, compared the efficacy and safety of the induction/maintenance strategy of 2

Table **2.** Selected Results of Trials in Antiretroviral-Naive Subjects

Study (Abstract No.) Description	Regimen/Study Arm (No. patients)	Baseline HIV-1 RNA (copies/mL)	Baseline CD4+ (cells/µL)	Plasma HIV-1 RNA Response (copies/mL)	CD4+ Change (cells/µL)	Comments
FORTE Trial (564) 48-wk study to evaluate the virologic benefit of an induction/maintenance strategy compared with standard 3-drug regimen	I/M therapy (n=62) 2 nRTIs, NNRTI, PI (24-32 wks) → drop PI at 24-32 wks[1] → 2 nRTIs, NNRTI	4.92 $\log_{10}$ (mean)	180 (median)	81% with <50, and 100% with <400 at wk 48	+172 (median)	Mean drop in HIV-1 RNA level significantly greater in the I/M arm. Grade 3 and 4 AEs similar in both arms.
	Standard therapy (n=60) 2 nRTIs, NNRTI	4.96 $\log_{10}$ (mean)	145 (median)	65% with <50, and 86% <400 at wk 48	+152[2] (median)	
Study 418 (570) 48-wk multicenter, open-label, randomized, comparative trial	Lopinavir 800 mg /ritonavir 200 mg qd (n=115)	4.8 $\log_{10}$ (median)	214 (median)	70% with plasma level <50	+185 (mean)	The qd group had a higher discontinuation rate (12% vs. 5%).
All patients received tenofovir/ emtricitabine	Lopinavir 400 mg/ritonavir 100 mg bid (n=75)	4.6 $\log_{10}$ (median)	232 (median)	64% <50	+188 (mean)	Grade 3 and 4 AEs were similar in both arms, both arms sustained similar increases in total cholesterol and triglyceride levels.
ABCDE Study (716) 48-wk, multicenter, open-label, randomized comparative trial	Lamivudine 150 mg bid or 300 mg qd/efavirenz 600 mg/stavudine 30 mg or 40 mg bid (n=122)	5.21 $\log_{10}$ (mean)	223 (mean)	64% <50 (ITT analysis) in both arms	+200 (mean increase in both arms)	At wk 48, stavudine arm had higher frequency of lipoatrophy than abacavir arm, both combined with lamivudine/efavirenz. More AIDS-defining events in the first 6 mo in abacavir arm.
Dose of stavudine depended on patient's weight	Lamivudine 150 mg bid or 300 mg qd/efavirenz 600 mg/abacavir 300 mg bid (n=115)	5.21 $\log_{10}$ (mean)	203 (mean)			
QD triple nRTI (51) 24-wk, pilot study to evaluate potency and safety of an qd regimen of 3 nRTIs Patients were excluded if they had K65R mutation	Didanosine EC 250 mg qd, tenofovir 300 mg qd, lamivudine 300 mg qd (n=24)	4.9 $\log_{10}$ (median)	133 (median)	0.61 $\log_{10}$ (overall median reduction at wk 12; n=20)	Not available	20 patients terminated early (median, 16 wks) due to a suboptimal response. Wk-12 resistance testing (n=20) showed 100% with M184I/V, 50% with K65R mutation.

continued, next page

Table **2.** Selected Results of Trials in Antiretroviral-Naive Subjects, continued

Study (Abstract No.) Description	Regimen/Study Arm (No. patients)	Baseline HIV-1 RNA (copies/mL)	Baseline CD4+ (cells/μL)	Plasma HIV-1 RNA Response (copies/mL)	CD4+ Change (cells/μL)	Comments
Tonus Study (52) 12-mo pilot study of qd regimen of triple-nRTI Primary endpoint was wk 48 plasma HIV-1 RNA <50 copies/mL. Study was prematurely interrupted due to high early virologic failure	Abacavir/ lamivudine/ tenofovir qd (n=40)	4.9 $\log_{10}$ (median)	221 (median)	33% virologic failure at wk 24 (>400)	Not available	Virologic failure in all patients with baseline HIV RNA-1 >4 $\log_{10}$ copies/mL. At wk 4, 86% had adequate C_{min} for all 3 drugs. 9/11 developed K65R and M184I/V mutations.
COL40263 (53) Preliminary evaluation of multicenter, open-label study of qd fixed-dose zidovudine/ lamivudine/ abacavir and tenofovir 22% of subjects discontinued early (8 due to elevated transaminases, 8 due to virologic nonresponse, HIV-1 RNA >400 copies/mL at wk 24)	Interim analysis of 88 subjects at wk 24	5.1 $\log_{10}$ (median) Required to have plasma HIV RNA >30,000 copies/ml	226 (median)	78% <400 copies/mL (wk 24)* 67% <50 (wk 24) *vs 51% in ESS30009 study	Not available	7/8 subjects with virologic failure had baseline HIV-1 RNA >100,000 copies/mL. 6/8 (75%) had wild-type virus at baseline; at wk 24, 13% had K65R, 25% remained wild-type.

[1] PI was stopped if 2 consecutive plasma HIV-1 RNA levels were below 50 copies/mL.

[2] The median increase in CD4+ count was not statistically different between arms.

[3] Statistically significant difference between the first 2 arms (P=0.05).

I indicates induction; M, maintenance; nRTI, nucleoside (or nucleotide) reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; EC, enteric coated; AE, adverse event; qd, once daily; bid, twice daily; ITT, intent-to-treat; wk, week; mo, month.

nRTI with 1 NNRTI and a PI administered for 24 to 34 weeks, followed by 2 nRTIs with one NNRTI, compared with standard therapy of 2 nRTIs and 1 NNRTI in antiretroviral therapy-naive patients. In the induction/maintenance strategy, the PI was stopped if 2 consecutive plasma HIV-1 RNA levels were below 50 copies/mL between weeks 24 and 32. The most common nRTI combinations were didanosine/stavudine (52%) and zidovudine/lamivudine (42%); the most common NNRTIs were nevirapine (64%) and efavirenz (36%); and the most common PIs were nelfinavir (71%) and lopinavir/ritonavir (27%). This study enrolled and followed up 122 patients with CD4+ counts greater than 25 cells/μL for a median of 81 weeks; at baseline the median CD4+ count was 180 cells/μL in the induction/maintenance group (n=62) and 145 cells/μL in the standard therapy group. Mean baseline plasma HIV-1 RNA levels in the induction/maintenance and standard arms were 4.92 $\log_{10}$ copies/mL and 4.96 $\log_{10}$ copies/mL, respectively. There were 17% and 25% of patients who had baseline plasma HIV-1 RNA levels greater than 300,000 copies/mL in induction/maintenance and standard therapy arms, respectively. Through week 24, 48% of patients in the standard therapy arm experienced virologic failure compared with 31% in the induction/maintenance arm (P=0.06); this

difference was even greater at or after 32 weeks (43% vs. 18%, $P = 0.002$). At week 48, 65% in the standard therapy arm and 81% in the induction/maintenance arm had plasma HIV-1 RNA levels less than 50 copies/mL ($P = 0.07$); the mean fall in plasma HIV-1 RNA level was 0.86 $\log_{10}$ copies/mL greater in the induction/maintenance arm ($P = 0.01$). The median increase in CD4+ count at 48 weeks was 172 cells/µL and 152 cells/µL in the induction/maintenance arm and the standard arm, respectively; the differences between the 2 treatment arms were not statistically significant. Only 5 patients were lost to follow up; by week 48, 83% of patients in the induction/maintenance arm and 84% of patients in the standard arm adhered to the assigned treatment. In the induction/maintenance group, 58% of patients stopped their PIs as planned at a median time of 26 weeks. The incidences of grade 3 or 4 adverse events were similar in both study arms, and they included elevation of liver enzymes, vomiting, and peripheral neuropathy. There was also no difference in the number of patients progressing to a new AIDS event or death. To interpret the efficacy of the induction/maintenance arm properly, a control arm using the maintenance regimen throughout the study would be needed.

Study 418

Gathe and colleagues (Poster 570) presented the week-48 results from the 418 study. This was a multicenter, open-label, randomized trial that compared the antiviral activity and safety of qd lopinavir/ritonavir and bid lopinavir/ritonavir in antiretroviral-naive, HIV-1 infected patients. A total of 190 patients with a screening plasma HIV-1 RNA level greater than 1,000 copies/mL and no CD4+ cell count criteria were randomized to receive lopinavir 800 mg/ritonavir 200 mg qd (n = 115), or lopinavir 400 mg/ritonavir 100 mg bid (n = 75). All patients received a backbone of qd tenofovir and emtricitabine. The overall median baseline plasma HIV-1 RNA level was 65,000 copies/mL, approximately 45% of patients had baseline CD4+ counts below 200 cells/µL, and 38% had a baseline plasma HIV-1 RNA level above 100,000 copies/mL. Over 20% of patients were women and about 55% were white.

At week 48, according to an intent-to-treat (ITT) analysis, the proportions of patients who achieved a plasma HIV RNA level below 50 copies/mL were 70% in the qd arm and 64% in the bid arm; the 95% confidence interval (CI) for the difference in responses between the 2 arms (-7%, 20%) met the protocol definition for non-inferiority of the qd regimen. No statistically significant differences were observed among the study arms with respect to the CD4+ cell count changes from baseline. Genotypic testing was performed for patients with plasma HIV-1 RNA levels above 500 copies/mL occurring at any time during week 12 to 24 (5 in each arm). There was no lopinavir or tenofovir resistance, and emtricitabine resistance emerged in 1 patient in each group.

Over 48 weeks, the proportion of subjects who discontinued the study was 19% in the qd and 25% in the bid arm; a higher rate of discontinuation due to adverse events was seen in the qd group (12% vs. 5% in the bid group), and higher rates of nonadherence and loss to follow-up were observed in the bid group (12% vs. 4% in the qd group). The most common adverse clinical event was diarrhea, which occurred in 16% in the qd arm and 5% in the bid arm ($P = 0.04$). There were no statistically significant differences in the proportions of grade 3 or 4 adverse clinical events between the 2 arms; laboratory hepatobiliary toxicity (elevation of transaminase levels) occurred in 5% and 3% of patients on the qd and bid regimens, respectively. Both arms sustained significant mean lipid elevations from baseline (in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels), but this did not result in significant changes in the 10-year coronary heart disease risk based on the Framingham Heart Study calculations.

Treatment of Antiretroviral-Experienced Patients

Lopinavir Inhibitory Quotient

Bertz and colleagues presented data correlating the lopinavir inhibitory quotient (C_{trough}/protein adjusted IC_{50}; IQ) and virologic response to two lopinavir/ritonavir-based salvage regimens (633 mg/166 mg or 400 mg/300 mg each with + 2 or 3 nRTIs) (Abstract 134). The patients were nRTI-, NNRTI- and PI-experienced and had a median fold-change in lopinavir IC_{50} of 4.1 (range 0.7-238). Overall, 58% of participants achieved a plasma HIV-1 RNA below 400 copies/mL, and this was similar in each arm. Details of the virologic outcomes will be presented at a future conference. In multivariate analyses, higher lopinavir IQs and more active nRTIs were associated with an improved virologic response. In contrast, lopinavir pharmacokinetic parameters were not associated with virologic response. This study provides evidence that higher doses of PIs may overcome resistance in some instances.

Lopinavir/Ritonavir vs. Atazanavir/Ritonavir

DeJesus and colleagues presented the 48-week results of a comparison of atazanavir plus ritonavir or saquinavir, with lopinavir/ritonavir in antiretroviral-experienced patients (Abstract 547). Subjects must have had more than 2 previous antiretroviral therapy regimens that included nRTI, NNRTI, and PI failure. They must have had a CD4+ count of more than 50 cells/µL and a plasma HIV-1 RNA above 1,000 copies/mL. Subjects replaced their failing PI with atazanavir/ritonavir (300 mg/100 mg qd), lopinavir/ritonavir (400 mg/100 mg twice daily) or atazanavir/saquinavir (400 mg/1000 mg qd) for 2 weeks. The nRTIs were then changed to tenofovir and an additional nRTI. The HIV-1 RNA at baseline was approximately 4.4 $\log_{10}$ in all 3 arms, and the median CD4+ counts were 317 cells/µL, 283 cells/µL, and 286 cells/µL, respectively.

Similar to the 24-week results presented previously, the atazanavir/saquinavir arm was found to be inferior to the other 2 arms at 48 weeks. The time-averaged change in plasma HIV-1 RNA from baseline was not different between the atazanavir/ritonavir and lopinavir/ritonavir arms. The change from baseline plasma HIV-1 RNA at week 48 was −1.93 $\log_{10}$ for the atazanavir/ritonavir arm and −1.87 $\log_{10}$

for the lopinavir/ritonavir arm. In 56% and 38% of the atazanavir/ritonavir arm HIV-1 RNA levels were below 400 copies/mL and below 50 copies/mL at 48 weeks, respectively, compared with 58% and 46% of lopinavir/ritonavir-treated subjects. The mean change in CD4+ count was 110 cells/μL and 121 cells/μL in the atazanavir/ritonavir and lopinavir/ ritonavir groups, respectively. Forty-nine percent in the atazanavir/ritonavir arm experienced elevations in bilirubin more than 2.5 times the upper limit of normal, compared with less than 1% in the lopinavir/ritonavir arm. The atazanavir/ritonavir arm was less likely to use lipid-lowering agents (8% vs. 19% in the lopinavir/ritonavir arm), and patients in this group had lower triglyceride levels (a 4% reduction from baseline compared with a 30% increase for the lopinavir/ritonavir arm) and total cholesterol (an 8% reduction from baseline compared with a 6% increase).

Lamivudine in Salvage Regimens

In vitro data suggest that the most common lamivudine-associated mutation, M184V, confers increased susceptibility to certain nRTIs, namely tenofovir, zidovudine, and stavudine, but not abacavir or didanosine. Consequently, lamivudine is often used in salvage regimens despite documented genotypic resistance. Dragsted and colleagues presented data on the use of lamivudine in salvage therapy for patients in whom a lamivudine-containing regimen was failing (Abstract 549). There were 133 subjects in whom a lamivudine-containing regimen failed. They were randomized to continue or to discontinue lamivudine in addition to starting a new antiretroviral regimen that was chosen prior to randomization.

At baseline, the median plasma HIV-1 RNA was 4.0 $\log_{10}$ copies/mL and the median CD4+ count was 310 cells/_L. At 48 weeks, 54 (83%) in the lamivudine arm and 60 (91%) of the no-lamivudine arm were still on their randomized treatment. There was no significant difference in the time-averaged change in HIV-1 RNA from baseline (−1.4 vs. −1.5 $\log_{10}$), percent below 400 copies/mL (66% vs. 65%), percent below 50 copies/mL (52% vs. 44%), or protocol-defined virologic failure. The M184V was maintained in more than 80% of subjects continuing to take lamivudine, but it was lost in the majority of the no-lamivudine arm (eg, present in <10% of follow-up samples tested).

Predictors of Response to Antiretroviral Therapy

Moore and colleagues presented data from the Johns Hopkins Cohort on the response to an initial antiretroviral regimen in HIV-infected persons over the age of 50 years (Abstract 556). Individuals over the age of 50 years were more likely to reach a plasma HIV RNA below detection than those aged 35 to 50 or younger than 35 (62.5% vs. 53.8% and 48.9%, $P = .01$), and were more likely to have durable virologic suppression (40.2% vs. 29.7% and 27.5%, $P = .01$). The CD4+ cell count changes were similar among the 3 groups. Mortality was significantly higher among those aged 50 or older, but this was primarily due to non-HIV related illness. Older age was also associated with an improved virologic response in AIDS Clinical Trials Group (ACTG) 388 (zidovudine/lamivudine plus: indinavir, efavirenz/indinavir, or nelfinavir/indinavir; Abstract 553).

Kaufmann and colleagues looked at CD4+ cell count rise in 326 participants in the Swiss HIV Cohort Study who maintained HIV-1 RNA levels above 1000 copies/mL for 5 years after an initial antiretroviral therapy regimen (Abstract 557). They found that 37.5% did not reach a CD4+ count of above 500 cells/μL at 5 years. This was associated with older age (odds ratio [OR] 3.0/10 years older) and with a lower baseline CD4+ cell count (OR, 0.54 per 100 CD4+ cells higher at baseline).

Triple-Drug Class Failure

Mocroft and colleagues (Abstract 554) presented data on behalf of the EuroSIDA study group. They examined the time to triple-drug class failure from enrollment in the cohort. At 6 years of follow-up, 24.1% of patients who were antiretroviral-experienced (ie, with monotherapy or dual therapy) prior to starting potent antiretroviral therapy had triple-drug class failure compared with 11.9% who were treatment-naive. Among patients who were treatment-experienced at baseline, prolonged exposure to nRTIs increased the risk of triple-drug class failure. Among patients who were treatment-naive, lower baseline CD4+ cell count and higher plasma HIV RNA level were associated with an increased risk of developing triple-drug class failure.

Changes in the Initial Antiretroviral Regimen

Moore and colleagues (Abstract 558) described the choices for initial antiretroviral regimens and the overall likelihood of virologic suppression from 1996 to 2002 among patients in the Johns Hopkins database. The use of a single, unboosted PI declined dramatically, from 85% in 1996 to 13% in 2001/2002. Concomitantly, there were increases in the use of NNRTI-based regimens (0% to 59%) and triple-nRTI regimens (0% to 16%). Ritonavir-boosted PI regimens accounted for 7% of initial antiretroviral regimens in 1996, 18% in 1997 and 1998, 15% in 1999 and 2000, and 13% in 2001-2002. These changes were associated with improved virologic outcomes. Forty-five percent of patients starting antiretroviral therapy in 1996 achieved a plasma HIV RNA below detection by 6 months compared with 73% who started in 2001 or 2002. Factors associated with achieving an HIV RNA level below detection by 6 months also included use of NNRTI or a boosted PI and no prior use of nRTIs.

Primary HIV Infection

Pilcher and colleagues (Abstract 20) reported experience with the Screening and Tracing Active Transmission (STAT) program conducted in North Carolina. In this study, North Carolina's 110 public HIV-testing sites added nucleic acid testing (NAT) to allow early detection of HIV-1 infection. Following enzyme immunoassay (EIA)/Western blot testing, antibody specimens were pooled 1:10:90 in pools of 100 specimens/pool and screened by NucliSens NAT. Acute infection was defined as HIV-1 RNA-positive and HIV-1 antibody negative. A

prevalence of HIV-1 infection of 56.7 per 10,000 was detected; of these, 21 individuals were diagnosed with acute infection. The NAT offered an additional 4.1% to the diagnostic yield of antibody testing (11.1% in jails, 6.4% in sexually transmitted diseases [STD] clinics). High transmission areas and factors associated with primary HIV infection in North Carolina were identified: rural and major urban areas and major tracking routes, male sex, men who have sex with men (MSM) status, multiple partners, African-American ethnicity, and age younger than 24 years. The STAT program offered a new model for increasing effectiveness of the volunteer counseling- and testing-based HIV surveillance and for targeting prevention programs.

Little and colleagues (Abstract 384) attempted to elucidate biologic factors that influence the relative transmissibility of certain viral variants from an HIV-1 infected source to a new index patient. It had been proposed (Derdeyn et al, 10th CROI, 2003) that the transmitted virus has more variable loop deletions in the *env* gene, and less neutralization resistance than most viruses from the donor individual. This study evaluated 10 patients with primary infection, within 50 days of seroconversion, and their 8 phylogenetically linked sexual partners. The *env* sequence of the source and the recipient patient clustered together and the genetic divergence between them was less than 2%. There were no significant differences between envelope lengths or the number of glycosylation sites between the source and the recipient partner. Neutralizing antibody responses were weak in both the source and the recipient, and wherever differences were seen, the recipient virus was more neutralization-sensitive. The authors concluded that neutralizing antibodies probably do not represent a critical factor in the selection of transmitted virus.

Ritola and colleagues (Abstract 386) investigated the viral complexity present during primary HIV-1 infection. The V1/V2 and V3 variable regions of *env* were determined for 109 subjects with primary infection, acquired mostly through homosexual contact (n = 95). Fifty-three percent of patients infected following homosexual contact had multiple V1/V2 variants; 57% of women versus 15% of men infected through heterosexual contact had multiple variants. Eighty-two percent of all subjects had a single V3 variant. Three percent of subjects had CXCR4-using variants. Based on these results the authors concluded that the type of mucosal surface exposed to the virus in combination with the sex of the transmitter influences the number of variants transmitted.

Lichterfield and colleagues (Abstract 393) evaluated the predominant target of early CD8+ T-cell response in 10 individuals with acute, early, and chronic infection. Ninety-four percent and 46% of the HIV-1 specific CD8+ T-cell responses were directed against Nef in patients with acute and chronic infection, respectively, and patients with untreated chronic infection had broadly diversified CD8+ T-cell responses. The patients with acute infection, who initiated therapy, maintained the immunodominance of Nef, and those who remained treatment naive after 1 year exhibited a steady increase in magnitude and breadth of HIV-specific CD8+ T cell responses. The authors postulate that this specificity of CD8+ T-cell responses during acute infection may become important in vaccine design.

Primary Infection: Response to Treatment

Voirin and colleagues (Abstract 23) presented data from 3 prospective primary HIV-1 infection cohorts in Lyon, Montreal, and Sydney. Patients (n = 203) were divided into 3 groups: starting antiretroviral therapy when symptomatic with acute retroviral syndrome (n = 51); starting therapy after the resolution of symptoms (n = 117); and receiving no therapy (n = 35). The mean overall baseline plasma HIV-1 RNA level was 4.49 $\log_{10}$ copies/mL, and they were not statistically different across study groups. After 3 years of follow-up, there were no differences in plasma HIV-1 RNA level and CD4+ cell count between patients who initiated antiretroviral therapy. The decay in plasma HIV-1 RNA level from baseline to 6 months was more dramatic in the group treated during acute retroviral syndrome, but this was not statistically significant ($P = 0.4$). The group that did not receive antiretroviral therapy had higher plasma HIV-1 RNA levels, and lower CD4+ cell counts at the end of a 3-year period.

Desquilbet and colleagues presented data on behalf of the French PRIMO study group (Abstract 397). They compared patients who initiated antiretroviral therapy within 6 months of seroconversion with patients from the SEROCO cohort who did not receive antiretroviral therapy after seroconversion. After adjusting for baseline plasma HIV-1 RNA level, patients who received 24 months of antiretroviral therapy followed by a 12-month treatment interruption had an estimated plasma HIV-1 RNA level of 3.75 $\log_{10}$ copies/mL compared with 3.94 $\log_{10}$ copies/mL in the untreated cohort. An adjusted analysis did not show a clear benefit of early treatment, and authors suggested that a randomized trial is needed to evaluate the long-term benefits of interruption of early antiretroviral therapy.

Primary Infection: Treatment Interruptions

Kaufman and colleagues (Abstract 24) presented follow-up data from the observational study of supervised treatment interruptions (STIs) during acute HIV-1 infection. Fourteen patients who were treated during acute infection and subsequently had a treatment interruption after virologic control followed by retreatment when plasma HIV-1 RNA remained above 5000 copies/mL for longer than 3 weeks (or was higher than 50,000 copies/mL at any point) have now been followed up for a median of 3.5 years. When treatment was stopped, only 11 patients maintained control of plasma HIV-1 RNA levels for at least 90 days. Only 3 patients achieved a maximal treatment interruption of 720 days, and they did not differ from the remaining patients by human leukocyte antigen (HLA) allele or baseline plasma HIV-1 RNA levels. The rate of CD4+ cell decline was variable. The rise in CD8+ T-cell response during the first, second, and third supervised treatment interruptions did not predict time to failure.

Hoen and colleagues (Abstract 395) presented the final results of the PRIM-

STOP pilot trial from France. Twenty-nine patients received a regimen of didanosine/stavudine/nelfinavir/hydroxyurea for 34 weeks, followed by 3 consecutive periods of 2, 4, and 8 weeks off antiretroviral therapy, separated by 12 weeks on treatment, discontinuation of antiretroviral therapy at week 84, and follow-up to week 108. Three patients were lost to follow-up. Of the 26 who completed the study all remained off therapy at week 108, and 1 had a plasma HIV-1 RNA level of less than 50 copies/mL. Only female sex was associated with a plasma HIV-1 RNA level of less than 1000 copies/mL at week 108. Three patients developed a major PI resistance (L90M) and hydroxyurea had to be stopped in more than half of the patients due to severe neuropathy.

Grey and colleagues (Abstract 399) evaluated virologic and immunologic predictors of initial response during structured treatment interruption in patients with acute and early HIV-1 infection. Lower baseline viral load and a shorter time to plasma HIV-1 RNA suppression on therapy were predictive of a longer time to rebound. Maintenance of a central pool of CD28+ CD8+ T-cells, rather than expansion of CD28+-effector T-cells, was associated with better control on therapy.

Superinfection

Several studies addressed superinfection during early HIV-1 infection. Smith and colleagues documented the frequency of HIV superinfection within clade B in a cohort of 56 antiretroviral-naive subjects deferring antiviral therapy (Abstract 21). The majority of the individuals were MSM. Superinfection was presumed where baseline and follow-up samples appeared phylogenetically distinct (mean 313, range 177–597 days apart). Evidence for superinfection was strengthened by clonal analysis and dye-primer length polymorphism analysis of HIV *env* and population-based *pol* sequencing. Superinfection was identified in 3 of 56 (6.5%) at 5 to 15 months after infection. In 2 cases, a wild-type strain was replaced by a resistant one. In the other, a drug-resistant virus replaced the wild-type strain. All individuals were men whose risk factor was homosexual exposure. Plasma HIV-1 RNA levels increased (mean 1.6 log increase) and CD4+ counts decreased (mean 132 cell/μL decrease) within 6 months of acquiring the superinfecting strain. It was estimated that superinfection occurred 5 to 13 months after the estimated date of primary infection.

Daar and colleagues (Abstract 394) described 1 patient initially infected with a multidrug-resistant subtype B HIV-1 virus who within 6 months of seroconversion had superinfection with a phylogenetically distinct, wild-type strain and had a modest increase in plasma HIV-1 RNA. Analyses of immune responses and sequence changes at several cytotoxic T lymphocyte (CTL) epitopes demonstrated that the new strain had a higher viral set-point but similar replicative capacity than the original strain; epitopes in Gag and Nef had key sequence differences in the superinfecting strain compared with the original HIV-1 virus. Distinct CTL responses were observed between the 2 strains, suggesting that this was more likely a distinguishing characteristic between the 2 strains than differences in replication capacities.

Similar data were presented by Gottlieb and colleagues (Abstract 454) using data from the Multicenter AIDS Cohort Study (MACS). Samples from 32 seroconverters were retrospectively evaluated using a combination of heteroduplex mobility assay, sequencing of the envelope C2-V5 region, and phylogenetic methods. Presumed superinfection with a second HIV-1 subtype B strain was detected in 1 individual (3%) at 1.3 years post infection. The newer isolate was also identified as an X4/syncitium-inducing phenotype. Within 6 months, there was rapid replacement of the initial virus by the superinfecting virus that was not explained by random genetic drift.

In 58 subjects from the Women's Interagency HIV study (WIHS) who reported or did not report injection-drug use (IDU), genetic differences in circulating HIV were evaluated (Abstract 952). Clonal analysis (≥5 clones/sample) of the HIV protease was made from samples with at least 10,000 HIV-1 RNA copies/mL. Among subjects with CD4+ counts above 650 cells/μL, genetic diversity was statistically significantly greater ($P < 0.03$) in IDU than among non-IDU subjects. This difference was not observed at lower CD4+ levels.

Pao and colleagues (Abstract 392) described the epidemiology of 104 individuals in the United Kingdom diagnosed with primary HIV infection (PHI) between 1999 and 2003. The median age was 36 years and 96% were men with 87.5% identifying MSM as their risk behavior and 6% identifying IDU as theirs. In the 3 months prior to PHI, 42% had 3or more sexual contacts and 34% had more than 1 STD. Thirteen of 104 (12.5%) had antiretroviral resistance. Phylogenetic analyses of pol identified 16 clusters from 35 individuals (97.5% MSM). Compared with non-clustered isolates, clustered isolates were more frequently derived from significantly younger individuals, and those who reported greater numbers of sexual contacts and higher rates of unprotected anal intercourse. The authors suggest these data may assist planning of future preventative strategies.

Sagar highlighted the stable coexistence of distinct HIV strains among untreated heterosexually-infected sex workers in Mombasa, Kenya (Abstract 385). Ten subjects were evaluated, 5 with relatively diverse envelope sequences and 5 with more homogenous sequences. Among the latter, significantly greater diversity was also observed among *gag* and *pol* sequences (average pairwise distances, $P < .001$). Further, these relationships were preserved over the ensuing 3 years in the 6 subjects with available data.

Treatment Strategies

Drug Reduction Strategies

Launay (Abstract 649) evaluated whether a strategy of reduced drug pressure could stabilize evolution of resistance in a multicenter pilot study in France. In the 26 subjects, a regimen including PI was failing, they had plasma HIV-1 RNA above 10,000 copies/mL, and they had drug resistance genotypes predicting activity of no more than 1 drug. All subjects were switched to

lamivudine with low dose indinavir/ritonavir 200 mg/100 mg bid. Pharmacokinetic management involved week-2 sampling of indinavir trough with adjustment to achieve a trough in the range 150 ng/mL to 350 ng/mL (using the estimated inhibitory quotient [IQ] of 0.5 for a multi-PI resistant virus). The median CD4+ cell change to 24 weeks was −49/μL ($P < 0.001$). However, the mean CD4+ count slope was equivalent to the slope in the 6 months prior to entry ($P < 0.001$). The median increase in plasma HIV-1 RNA was 0.22 $\log_{10}$ copies/mL. However, 16 of 25 subjects had trough indinavir values below 150 ng/mL, requiring corrective dose adjustment of indinavir to 400 mg bid. Resistance profiles were reported as being stable for the duration of the study. A cost-reduction of antiretroviral therapy of 76% per day was reported.

Late Intensification: The Addition of Abacavir to a Stable Treatment Regimen With Sustained Plasma HIV-1 RNA Level Suppression.

Hammer and colleagues (Abstract 56) presented the results of ACTG 372A. This was a randomized, double-blind, placebo-controlled trial enrolling 229 individuals with plasma HIV-1 RNA levels of less than 500 copies/mL and who were on stable therapy with zidovudine (or stavudine)/lamivudine/indinavir at 800 mg 3 times a day (tid). Subjects were randomized to continue their therapy and add abacavir or abacavir placebo. The composite endpoint was the time to virologic failure (confirmed HIV-1 RNA >200 copies/mL) or permanent treatment discontinuation. The median baseline CD4+ counts in the abacavir and abacavir placebo arms were 245 cells/μL and 252 cells/μL, respectively. A total of 180 subjects (79%) completed the study, with 124 (54%) completing the study on their assigned treatment. The median follow-up time was 227 weeks. Comparing the 2 study arms, there were no differences in CD4+ count increases during follow-up. Nor were there differences in the proportions with virologic failure (ITT log rank $P = 0.2$), with HIV-1 RNA levels below 50 copies/mL or with HIV-1 RNA levels below 6 copies/mL at 48 weeks (n = 98). Nor were there differences in the levels of proviral HIV-1 DNA in subjects in each arm with sustained suppression of HIV-1 RNA levels below 50 copies/mL (n = 82). Among 69 subjects experiencing virologic failure, resistance testing demonstrated no significant differences in the relative frequencies of K65R (0%, 0%), L74V (0%, 7%), and M184V (41%, 41%) in the abacavir and placebo arms, respectively. Nephrolithiasis (overall, 17%) was observed in 14 abacavir recipients and 26 abacavir placebo recipients ($P = 0.037$). The authors suggest that these results do not support a strategy of late intensification with abacavir in those with stable plasma HIV-1 RNA level suppression.

Structured Treatment Interruptions in Antiretroviral-Experienced Persons

The Community Programs for Clinical Research on AIDS (CPCRA) 064 study previously demonstrated the lack of benefit of 4-month structured treatment interruption (STI) prior to starting a new regimen in subjects with moderately advanced disease. Lawrence and colleagues (Abstract 665) described the changes in genotypic resistance patterns in those with STIs that were 4 months or more (n = 93), 2 to 4 months (n = 28), and for less than 2 months (n = 8). STI termination prior to 4 months was recommended if the CD4+ count fell more than 50% from baseline to follow-up. In the group with STI of 4 months or more, the mean HIV-1 RNA levels were significantly lower than the means of the other 2 groups (4.9 log copies/mL versus 5.3 $\log_{10}$ copies/mL, respectively; $P = 0.003$). Longer STI (≥ 4 months) was associated with greater reduction in the number of major mutations (from 9.9 to 4.5) and an increase in the mean number of drugs to which the virus was susceptible (from 2.0 to 9.8).

Benson and colleagues (Abstract 58) presented the week-48 results of ACTG 5806. In this study, 41 patients with a plasma HIV-1 RNA level greater than 5,000 copies/mL, and a history of virologic failure on at least 2 prior antiretroviral regimens, were randomized into 1 of 2 treatment arms: 16-week structured treatment interruption (STI) followed by an optimized antiretroviral regimen that was selected based on results of resistance testing (n = 21); or immediate initiation of optimized antiretroviral therapy (n = 20). The primary endpoint was plasma HIV-1 RNA level below 400 copies/mL at week 48. The median baseline CD4+ count and plasma HIV-1 RNA level were 225 cells/μL and 38,000 copies/mL, respectively. At week 48, the proportion of subjects with plasma HIV-1 RNA levels below 400 copies/mL was 19% and 33% in the STI and no-STI arms, respectively ($P = 0.44$); the median drop in plasma HIV-1 RNA level was 0.65 $\log_{10}$ in the STI arm, and 1.15 $\log_{10}$ in the no-STI arm (P = not significant). The median increase in CD4+ count from baseline was 10 cells/μL and 17.5 cells/μL in the STI and no-STI arms, respectively. In the STI arm, 18 subjects had genotypes performed at end of the treatment interruption; reversion of baseline mutations was seen in 5 of 18, partial reversion in 7 of 18, and little or no reversion in 6 of 18 patients. At week 48, in patients with virologic failure despite reversion of baseline mutations, phylogenetic analyses demonstrated that resistance mutations clustered with the virus population at entry and not at the end of the STI. Three-drug class resistance occurred in patients with virologic failure despite antiretroviral therapy with only 2 drug classes, indicating linkage of mutations on the same genome. The authors concluded that the persistence of resistant virus despite STI is a likely explanation for the ineffectiveness of STI in patients with multidrug-resistant HIV-1.

Calvez and colleagues (Abstract 661) compared the rates of reversion to wild-type virus at 26 weeks, by antiretroviral class, in 19 subjects with stable on-treatment viremia. The median CD4+ count was 61.5 cells/μL and the median HIV-1 RNA was 5.1 $\log_{10}$ copies/mL. The median number of nRTI, NNRTI, and PI mutations was 7, 2 and 4, respectively. The shift to wild-type virus was faster for PIs, intermediate for NNRTIs, and slowest for nRTIs ($P < 0.05$). Reversion at reverse transcriptase codons 41, 215, and 219 was uncommon. These data underline the complex dynamics of the circulating, resistant HIV quasispecies.

The Emergence of Drug Resistance With Repeated STIs

With the exception of the Agence Nationale de Recherches sur le Sida (ANRS) 097 study in experienced persons with virologic failure, trials have largely failed to demonstrate clinical benefit to STIs. However, interruptions in therapy do occur in clinical practice for a variety of reasons. The potential risks of treatment interruptions in relation to the emergence of resistance were highlighted by several presentations at the conference.

The ISS PART study (Abstract 552) is an ongoing, randomized, multicenter clinical trial comparing continuous versus intermittent therapy in 273 subjects with plasma HIV-1 RNA below 400 copies/mL who are on a stable first regimen. An STI strategy was undertaken by 136 subjects comprising 4 STIs of 1, 1, 2, and 2 months each separated by 3 months of treatment. Of these subjects 39 (29%) had resistance mutations at STI. Among nRTI-treated subjects, 136 (3%) had the T215Y mutant; of those taking lamivudine, 123 (16.3%) developed M184V; of PI-treated subjects, 59 (10.2%) developed L90M or M46I; and of those on NNRTIs, 101 (7%) developed K103N. Of the 39 subjects with mutations, 11 (28%) were detected in lymphocyte DNA prior to the STI. The proportion with virologic failure (HIV-1 RNA >400 copies/mL at the end of treatment phase) was greater for those demonstrating mutations than for those without mutations, 13 of 39 (33%) and 12 of 97 (12.4%), respectively (P = 0.004).

Antiretroviral Drug Resistance and Replication Capacity

Transmission of Drug-Resistant Virus and Prevalence Studies of Drug Resistance in Treatment-Naive Patients

For the Options project, Kozal (Abstract 35LB) described transmission-risk behavior patterns in HIV-infected individuals and their relationship to the potential transmission of drug-resistant virus. Of the 333 subjects enrolled between 2000 and 2003 98 (27%) had resistance to at least 1 class of drug. Of those followed up for more than 6 months, 19 had drug resistance and engaged in sex with an HIV-seronegative or serostatus-unknown partner. These individuals engaged in 423 such events representing 38% (423 of 1,116) of all high-risk sex events. These data suggest that a likely source of transmitted resistance is a small core group of individuals in clinical care with known resistance and ongoing HIV transmission behaviors.

Little and colleagues (Abstract 36LB) described the persistence of transmitted drug-resistant virus among subjects with PHI who deferred antiretroviral therapy. Twelve subjects were identified. The median follow-up, plasma HIV-1 RNA, CD4+ count, and replication capacity were 310 days, 5.2 $\log_{10}$ copies/mL, 542 cells/μL and, 84%, respectively. NNRTI, PI, and nRTI resistance was observed in 10, 4, and 5 subjects, respectively. Reversion of resistance was seen infrequently; 1 of 10 isolates with K103N reverted to N103K/N and 3 of 5 nRTI mutants also reverted (T215F⇒T215Y/C [n=1], M184V⇒V184M or M/V [n=2 of 5]). Further, the time for these events to occur was long, a median of 362 days. No reversion of PI resistance mutations was observed.

For the Duke-University of North Carolina-Emory PHI Consortium, Hicks and colleagues (Abstract 682) described the primary phenotypic resistance profiles in 30 residents of North Carolina with PHI diagnosed between January 1998 and January 2003. Resistance comparisons for seroconversions up to June 2000 (n=12) and from July 2000 (n=18) were made. Resistance was more common with seroconversions up to June 2000 (P=.018) and for whites compared with all others (P=.018). Overall 4 of 30 subjects had resistance to at least 1 drug; all 4 were diagnosed prior to July 2000. The authors noted an apparent reduction in the rate of transmitted resistance more recently.

A complementary presentation by de Mendoza noted an overall reduction in the rate of transmitted resistance in 128 consecutive newly HIV-infected individuals seen between January 1997 and December 2003 in 4 clinics in Spain (Abstract 681). Of these subjects, 19 (15%) had genotypic evidence of resistance; and 18, 2, and 4 had nRTI, NNRTI, or PI resistance mutations, respectively. The rates of drug resistance in 1997 and 2003 were 33.3% and 10%, respectively. The authors noted a negative correlation with yearly rates of those with plasma HIV-1 RNA below 50 copies/mL and those of primary drug resistance, (r = -0.87, P = 0.054).

Yerly and colleagues (Abstract 680) struck a cautionary note concerning interpretation of changes in the prevalence of transmitted drug resistance. This group evaluated factors modulating the prevalence of resistance within the Swiss HIV cohort. There were 505 subjects with HIV seroconversion diagnosed between January 1996 and December 2003 who were evaluated. Overall, nRTI mutations were most frequently seen, and among these, the most common change was at codon 215 (17 of 31; 55%). Factors impacting prevalence included clustering of resistance (5 subjects in Lausanne in 2001 with mutations M41L/T215D); the influx into this population of non-B subtypes with lower levels of resistance; and the absolute HIV-1 RNA level, with greater proportions of subjects in care with plasma HIV-1 RNA below 400 copies/mL.

Cane reported long-term resistance profiles in 16 patients with resistance mutations noted at primary infection (Abstract 684). Three of these 16 patients were infected with virus resistant to 3 classes, and 2 of the 16 had NNRTI resistance only. Mutations at reverse transcriptase codons 41, 69, 215, and 219 were seen in 5, 4, 6, and 3 subjects, respectively. The median time to follow-up sequencing was 20.5 months (range, 2-120), at which time resistance patterns remained stable on no therapy. Loss of only 3 mutations was observed at follow-up: V62A, C181Y, and Q219K. One further isolate demonstrated a switch from T215Y→C concurrent with a 10-fold increase in HIV-1 RNA.

For the CASCADE cohort (Concerted Action on Seroconversion to AIDS and Death in Europe), Masquelier described the complete resistance profiles of 432 subjects for whom resistance testing was performed within 18 months of seroconversion (occurring between 1987 and 2003; Abstracts 683, 684). Transmitted resistance was observed in 54 of 432 (12.5%) individuals. In 47 of

54 (87%) resistance was to one class (34 to nRTI, 8 to NNRTI, and 5 to PI); in 1 of 54 (2%) there was resistance to 3 classes. Non-subtype B strains were more recently observed (after August 1999) and more likely to occur as a result of heterosexual transmission. A trend toward more frequent resistance over time was noted ($P = .07$).

Bezemer and colleagues (Abstract 679) described limited recent prevalence of drug resistance in 100 newly diagnosed HIV infections in Amsterdam from 1994 to 2002. From 1996 onward, only revertants at reverse transcriptase codon 215 were seen. Prior to 1998, 20% of new infections had genotypic evidence of resistance compared with 6% from 1998 onward. The median plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL compared with 5.0 $\log_{10}$ copies/mL in drug resistant versus non-resistant isolates, respectively ($P = .036$).

The Impact of Transmitted Resistance on First Regimen Outcome

Borota-Esoda (Abstract 672) examined the impact of baseline resistance in an international study of antiretroviral-naive subjects receiving efavirenz/didanosine with either emtricitabine (n = 285) or stavudine (n = 285). The authors evaluated baseline resistance in those subjects followed up to week 60 and who were unable to achieve, or rebounded from, plasma HIV-1 RNA levels below 400 c/mL. Among these 546 subjects, baseline genotypic resistance to nRTI, NNRTI, or both classes was seen in 6.2%, 8.8%, and 1.5%, respectively. For both study arms, the proportions with virologic failure were significantly greater in these arms with resistance to NNRTIs, nRTIs, or both classes. For those in the emtricitabine/didanosine/efavirenz arm, the proportion with treatment failure with K103N at entry was 43% and without K103N was 4% ($P = 0.001$). For those in the stavudine/didanosine/efavirenz arm, the proportion with treatment failure with the K103N at entry was 71% and without K103N was 12% ($P = 0.001$).

The impact of transmitted resistance on therapy outcome was also evaluated by Pillay within the CASCADE study reported above (Abstract 685). Among the 199 persons starting therapy between June 1996 and June 2003, 26 (13.7%) had genotypic evidence of resistance. The most common mutations were at codons 41 (n = 9) and 215 (n = 15). The median time from infection to initiation of potent antiretroviral therapy was 244 days. At a median time on therapy of 94 days, 90% of subjects had plasma HIV-1 RNA below 500 copies/mL. No difference in virologic success was observed between those with and without resistance. The authors speculate that primary resistance may complicate later treatment failure.

Resistance Following Sequential Regimens

The rates of resistance at baseline and at follow-up on sequential antiviral regimens were explored by Johnson and colleagues in ACTG 384 (Abstract 662). This study evaluated a variety of linked first and second regimens in antiretroviral-naive subjects. The first nRTI combinations were either stavudine/didanosine or zidovudine/lamivudine. The nRTIs were coadministered with efavirenz, nelfinavir, or both. Resistance mutations were observed at baseline in only 1% (10 of 899) subjects. Among those receiving 3 drugs, 44% to 72% of subjects had virologic failure with wild-type HIV sequences. Thymidine analogue-associated mutations (TAMs) were seen at failure in approximately 3% of all regimens, and K65R and L74V were each seen in 4% of stavudine/didanosine failures. Among the treatment arms, those starting with zidovudine/ lamivudine/efavirenz had the lowest rate of failure but not the lowest rate of resistance mutations at failure (15 of 31, 48%). The lowest proportion of resistance mutations at failure was observed in the stavudine/didanosine/nelfinavir arm (22 of 77, 29%).

Treatment-Experienced Patients

Abacavir. The Zodiac study (CNA30021; Abstract 551) compared two regimens of abacavir/lamivudine/efavirenz in which abacavir was given either qd or bid. Virologic failure (>50 copies/mL HIV-1 RNA) was observed in 10% in the abacavir qd arm and 8% in the bid arm to 48 weeks. Noninferiority of the abacavir qd arm was previously presented. Of these only 31 of 70 (44%) had an HIV-1 RNA level sufficient for resistance testing (ie, >400 copies/mL). Among these a non-significant trend toward greater numbers of mutations in the qd arm was observed. Among those with resistance data available 12 of 16 in the qd arm and 14 of 15 in the bid arm developed the K103N mutation. Also, in the qd arm 10 of 16 developed the M184V mutation compared with 5 of 15 in the bid arm.

Irbeck and colleagues (Abstract 661) compared the resistance profiles in 649 antiretroviral-naive subjects with treatment failure of efavirenz/lamivudine with either abacavir or zidovudine (CNA30024). Virologic failure (consecutive plasma HIV-1 RNA levels >50 copies/mL) was uncommon in this study (6% in the abacavir group and 4% in the zidovudine group). Post-failure genotypes were obtained in 13 of 20 in the abacavir and 10 of 13 in the zidovudine arms. Of these samples, 11 were wild-type and 12 had resistance mutations (NNRTI mutations in 12 of 12 samples and M184V in 10 of 12 samples). No TAMS were observed.

Didanosine. Clavel and colleagues (Abstract 670) explored the degree to which TAMs affect antiviral activity of and susceptibility to didanosine in a recombinant virus assay (AI454-176, Jaguar trial). Patients with stable on-treatment viremia were randomized to add didanosine (n = 110) to their therapy or not (n = 58). Genotypic and phenotypic predictors of week-4 change in HIV-1 RNA were evaluated. The distribution of didanosine fold changes at baseline was narrow, with only 23% and 13% of values above 2.0 and 2.5, respectively. Only a weak correlation was found between didanosine fold changes at baseline and week-4 change in HIV-1 RNA. However greater numbers of the specific mutations M41L, T215Y/F, L210W, K219Q/E, L74V, and T69D were associated with reduced virologic response ($P < .001$). The authors suggested that genotype may be a more useful predictor of in vivo didanosine activity.

Atazanavir. Colonno and colleagues (Abstract 656) examined the evolution of phenotypic and genotypic atazanavir resistance profiles in 100 treatment-

experienced subjects who received a variety of atazanavir-, atazanavir/r- or atazanavir/saquinavir-containing regimens. Of these 100 isolates, 18 developed the signature atazanavir mutation I50L. Over half of those developing I50L had resistance to only 1 or no other PIs at baseline. Among these 18 isolates the only major baseline PI mutation observed was the L90M. Mutations coemergent with I50L were L33/V/F (in 5), E34K/Q/A (in 6), M36I/V/L (in 6), K45R (in 4), A71V/T/I (in 10), G73S/T (in 7) and V82A/F/T (in 3). Thus the emergence of I50L with atazanavir in treatment-experienced subjects is associated with a lack of PI cross-resistance at baseline.

Resistance to atazanavir by the I50L mutation. Weinheimer examined the resistance profiles and protease activity associated with the sentinel atazanavir mutation I50L in wild-type and mutant backgrounds (Abstract 625). Using the NL4-3 reference strain, the authors noted augmentation of I50L atazanavir resistance by the A71V mutation. The I50L mutant (+/– A71V) conferred fold changes of above 0.4 to all PIs except amprenavir. In isolates bearing A71V with either D30N, G48V, V82A, I84V, or L90M, the introduction of I50L was associated with general reductions in the levels of resistance to PIs with the exception of amprenavir, which was impacted only slightly. Protease activity in the absence of drug and measured as percent p24/p25 demonstrated that the I50L-A71V motif impaired protease activity in wild-type and mutant protease. Thus, I50L mutant (+/– A71V) appears to impair protease processivity and to enhance susceptibilities to most PIs, with more neutral effects being observed for amprenavir.

TMC114. Using a panel of 5,061 isolates, including 2,202 protease resistant isolates, De Mayer compared the susceptibilities to the PI TMC114 and compared these with those of approved PIs (Abstract 620). Isolates were grouped by the number of specific PI mutations: D30N, M46I/L, G48V, I50V, V82A/F/T/S, I84V, and L90M. Among isolates with 3 or more mutations the proportions susceptible (<4-fold change) to TMC114, amprenavir, saquinavir, atazanavir, and lopinavir were approximately 55%, 21%, 22%, 17%, and 5%, respectively.

Fusion inhibitors. Enfuvirtide (T-20) is a synthetic 36–amino acid peptide corresponding to residues 127 to 162 of gp41. Enfuvirtide resistance is associated with changes in amino acids 36 to 45 of the HR1 domain. Xu studied the evolution of genotypic changes in the HR1 and HR2 domains (Abstract 659). Samples were derived from 17 highly treatment-experienced patients with virologic failure on an enfuvirtide-containing regimen. Mutations in HR1 were noted in all cases, including the previously unreported changes N42Q/H and N43Q. Continued evolution of HR1 mutations was observed. Six of 17 (35%) patients developed an S138A substitution in the HR2 domain after emergence of HR1 mutations (typically at position 43). Four patients demonstrated the loss of both HR1 and HR2 mutations following cessation of enfuvirtide therapy.

Monachetti evaluated clinical samples, at baseline and at follow-up, derived from 8 individuals with virologic failure on enfuvirtide-containing salvage therapy (Abstract 660). A modified NL4-3 recombinant bearing the test isolate's gp41 sequence spanning the HR1 and HR2 domains was used. In the recombinant phenotyping assay greater than 100-fold decrease in susceptibility (ie, resistance) from baseline was observed in 7 of 8 isolates after at least 9 months of therapy. Only 2 of 7 clinical isolates had greater than 50% reductions in drug-free replication capacity (RC) from baseline. Site-directed single mutations conferred significant resistance to enfuvirtide. However, such mutations conferred at most only modestly lower RCs (eg, 60% to 80% were observed with single changes at codons 43, 45, or 72).

Tenofovir resistance and K65R. The K65R mutation is the signature resistance mutation arising with tenofovir and may confer cross-resistance to all nRTIs except zidovudine and stavudine. Several presentations focused on the characteristics of this mutation (Abstracts 54, 55, 626, 627, 637).

Amiel noted the prevalence of K65R mutants in 24 of 3025 (0.8%) samples sequenced within a French database covering the last 5 years (Abstract 627). M184V was present in 8 (44%) of these samples. The Q151M mutation associated with multi-nRTI resistance was seen in 9 (50%) samples. By comparison, the overall prevalence of Q151M in this database was 33 of 3025 (1%); thus, among samples with Q151M, 9 (44%) had K65R concurrently. The authors comment that the overall rarity of the K65R and Q151M mutations alone, but relatively high co-occurrence, raises concerns for coselection and represents a potential pathway for cross-resistance distinct from TAMs. The prevalence of K65R is likely to increase with the widespread use of tenofovir.

The impact of K65R on viral fitness was evaluated using 4 primary isolates in which this mutation arose during tenofovir therapy (Abstract 637). Growth was compared with pretherapy isolates and to 2 reference strains. Comparative growth curves in the setting of increasing tenofovir concentrations demonstrated the relative growth advantage of K65R isolates over pretherapy isolates. However, competition cultures in a drug-free environment demonstrated the marked growth impairment of K65R isolates relative to both the control isolates and baseline isolates. These data confirm prior observations that K65R impairs viral fitness.

Two presentations focused on mechanistic aspects of K65R as a resistance mutation. White demonstrated that compared with wild-type enzyme, a reverse transcriptase with K65R exhibited both decreased incorporation of tenofovir, abacavir, stavudine, and zidovudine (5- to –17-fold less) and variably decreased excision of incorporated drug (Abstract 55). This reduced excision effect was most apparent for zidovudine, being 43% for wild-type and 19% for the K65R mutant in the presence of the next appropriate nucleotide. The authors suggested that for a given drug the relative interactions of diminished binding and excision in the setting of K65R are responsible for the observed phenotypes.

A complementary study by Parikh and colleagues (Abstract 54) observed that the frequency of K65R increased from 0.8% to 3.8% from 1998 to 2003 among 65,000 samples in a commercial

database. Within this dataset a negative correlation was observed between K65R and the TAM cluster M41L/L210W/T215Y. In vitro, recombinant isolates bearing K65R were 2.5- to 10-fold resistant to nRTIs tested except those with a 3'azido moiety (eg, zidovudine), which demonstrated wild-type sensitivity. Furthermore recombinants with M41L/L210W/T215Y or 67N/70R/T215F/K219Q with K65R demonstrated reduced zidovudine resistance (approximately 3-fold with K65R versus greater than 30-fold without K65R) and also reduced primer unblocking (wild-type activity with K65R versus approximately 10-fold without K65R). Thus K65R was demonstrated to antagonize both the mechanism and expression of zidovudine resistance. These data may help explain the observed low rate of concurrent selection of TAMs and K65R.

Other Factors

Hypersusceptibility. ACTG 368 compared the activities of efavirenz/indinavir/abacavir and efavirenz/indinavir in nRTI-experienced, PI-naive subjects (Abstract 669). NNRTI-experienced subjects (n = 26) received open label efavirenz/indinavir/abacavir. NNRTI-naive subjects received efavirenz/indinavir with abacavir (n = 140) or without abacavir (n = 143). At week 16 there were no differences in the rates of virologic failure in abacavir and no-abacavir arms, being 27% and 31%, respectively ($P = 0.5$). Within this study Demeter and colleagues evaluated the impact of baseline drug resistance on 16-week virologic outcomes. The phenotypic susceptibilities were measured in a multiple cycle assay. The impact of specific baseline reverse transcriptase mutations previously associated with efavirenz hypersusceptibility, including T215F/Y, D67N, H208Y, and L210W, was also evaluated. At baseline, 37% of subjects had a greater than 3-fold change in susceptibility to abacavir. Neither the baseline abacavir susceptibility nor the overall phenotypic susceptibility score were predictive of virologic failure. However, virologic failure was significantly less common if 2 or more efavirenz hypersusceptibility mutations were present ($P = 0.0017$). Notably, in a small number of individuals on indinavir/efavirenz only, the L74V reverse transcriptase mutation was coselected with K103N and L100I.

Haubrich and colleagues (Abstract 671) evaluated the impact of baseline hypersusceptibility to delavirdine in representative samples from 96 subjects in ACTG 359. This study evaluated the following regimens in 185 nRTI-experienced subjects: delavirdine/saquinavir sgc with either ritonavir, ritonavir/adefovir, nelfinavir, or nelfinavir/adefovir. Virologic response, evaluated at weeks 4 and 16, was defined as a plasma HIV-1 RNA at or below 500 copies/mL. In all models, the entry plasma HIV-1 RNA level was predictive of virologic response. Delavirdine hypersusceptibility defined by a cutpoint 0.4 fold or lower, or on a continuous scale, was predictive of virologic success at week 4 but not week 16. Using data from a logistic regression model, the authors suggested that the optimal cutpoint for delavirdine hypersusceptibility is 0.3- to 0.4-fold or lower.

CXCR4 Coreceptor studies. HIV that utilizes the CXCR4 coreceptor (when present, the virus is termed X4 virus), or that induces syncytia (SI virus), has been associated with accelerated progression of HIV disease. Jensen and colleagues (Abstract 415) utilized previously described position-specific scoring matrices (PSSM) to assess V3 sequences for both X4 and SI potential. They applied this matrix to early samples from 32 seroconverters in the MACS to evaluate whether rapid progressors are characterized by early acquisition of X4/SI virus. Twenty-one of 32 were rapid progressors and 3 of 21 had X4 virus, 2 of these being dually infected compared with 0 of 11 standard progressors. A correlation was noted between preinfection CD4+ counts and PSSM score (P = 0.031). Mean and maximum SI scores were also higher in rapid progressors ($P < 0.016$). Analyses suggested that mean SI score influenced progression independently of dual infection ($P = 0.027$).

Mosier (Abstract 409) described multiple independent coreceptor switch variants that were selected from 6 R5 (ie, virus containing the CCPR coreceptor) parental strains after 12 to 120 days of culture in mixtures of cells expressing CCR5 or CXCR4. As these viruses transitioned to X4, the susceptibility to CCR5 and to CXCR4 inhibitors increased, suggesting less efficient coreceptor use as an obstacle to switching. Further, replication was less efficient and infectivity was impaired for switch variants, suggesting loss of fitness as a further obstacles to switching.

UK-427,857 is a novel CCR5 antagonist in development. A concern regarding in vivo use of R5 antagonists is the possible selection for X4 variants during treatment. Westby described a patient harboring distinct R5, X4, and dual-tropic variants when inadvertently enrolled in a phase IIa, 10-day monotherapy study (Abstract 538). The patient experienced no drop in plasma HIV-1 RNA despite measurable drug exposure and ex vivo UK-427,857 CCR5 receptor occupancy within the anticipated range. Clonal sampling showed a shift from a mixture of viruses using R5 and R5X4 coreceptors at baseline to a mixture of viruses using X4 and R5X4 at day 11. Reversion to R5 predominance was observed after UK-427,857 was stopped.

The potential clinical relevance of X4 tropic viruses was highlighted in a presentation from Solomon (Abstract 654). Eleven subjects had on-treatment viremia over at least 12 months; 5 had declining and 6 had rising CD4+ counts. All individuals had at least 1 major mutation in protease or reverse transcriptase associated with resistance. Thymic growth of lymphocyte derived isolates was equivalent between the 2 groups. However replication in lymphocytes and CD4+ depletion was greater in isolates derived from nonresponders ($P < 0.05$). Further, for infected and uninfected CD4+ T-cells, apoptosis was greater by isolates derived from nonresponders ($P < 0.001$). X4 tropism was demonstrated in 4 of 5 non-responders and 2 of 6 responders. These data underline the potential relevance of X4 tropism in the clinical setting.

Observational cohort studies. Hogg and Harrigan (Abstracts 674, 689) described the prevalence of drug resistance among subjects followed up in British Columbia between August 1996 and September 2000 (The Homer Cohort). Within this cohort of 1,388 individuals,

the median follow-up time was 52.7 months. Genotypic evidence of drug resistance was observed in 393 individuals; resistance to lamivudine, other nRTIs, NNRTIs, and PIs was seen in 68%, 35%, 50%, and 27% of subjects, respectively. During follow-up, 238 subjects died (crude mortality rate, 17.2%); among these individuals, resistance to 1, 2, or 3 classes, to lamivudine, to NNRTIs, to other nRTIs; or to PIs was seen in 15%, 13%, 1%, 19%, 18%, 8% and 3%, respectively. No resistance was seen in 71% of subjects who died. Among those with a minimum follow-up time of 12 months and using multivariate analyses that controlled for other contributory variables, individuals with NNRTI resistance had death rates that were 2.74 times higher (range, 1.55-4.84; $P < 0.001$) than those without such resistance. This association should be interpreted cautiously.

Fessel analyzed 3,320 sequences from 2,324 persons in Northern California who had genotypic resistance testing between 1998 and 2002 (Abstract 690). Outcomes after resistance testing were analyzed. Eighty-two subjects (3.5%) had 3-class resistance (intermediate or high-level resistance to all 18 FDA-approved HIV drugs/formulations). In 324 (13.9%), 2-class resistance was detected (intermediate or high-level resistance within 2 drug classes with complete susceptibility to a third class). Of this group 74 (23%) had PI and nRTI resistance. Three-class resistance occurred almost exclusively in those with more than 4 years of prior therapy. Among those with 3-class resistance, sustained or transient virologic responses to salvage therapy were seen in only 10% and 18%, respectively. Among those with PI and nRTI resistance introduction of an NNRTI-based regimen reduced plasma HIV-1 RNA to below 50 copies/mL in 53%. This was sustained in only 36% of these individuals among whom NNRTI-associated resistance emerged on viral rebound.

Low-Level Viremia and Viral Persistence

Various studies evaluated the relevance of preexisting minority variants to ongoing therapy (Abstracts 37, 39, 57). Mellors and colleagues (Abstract 39) evaluated the relevance of preexisting minority variants to treatment failure associated with efavirenz resistance. The 11 NNRTI-naive and 12 NNRTI-experienced subjects were enrolled in ACTG 398 and did not have NNRTI mutations at entry by standard sequencing techniques. Single genome sequencing demonstrated baseline NNRTI mutations in 6 of 11 NNRTI-experienced patients with the following frequencies per positive patient: Y181C and G190A (5/15 sequences); Y181C (3/19); Y181C (3/22); V108I (2/35); K103N (1/33); and K103N (1/34). By comparison, NNRTI-resistant variants were found in only 2 of 12 NNRTI-naive patients: L100I and P225L (1/33 sequences each) and K103N (1/41 sequences). In 5 of 6 NNRTI-experienced patients phylogenetic analyses showed clustering of the baseline and failure of NNRTI-resistant variants. In the 2 NNRTI-naive patients, the baseline K103N variant clustered with the failure genotype but the L100I and P225L variants did not. These various studies supported the concept that in the absence of drug pressure, preexisting mutants may continue to circulate below the limits of detection by current assays.

Martin (Abstract 653) described correlates of CD4+ cell count changes over time in 47 subjects on stable antiretroviral therapy, with stable plasma HIV-1 RNA of at least 100 copies/mL for at least 12 months and with resistance to at least 1 drug, in the Study of the Consequences of the Protease Inhibitor Era (SCOPE). At baseline, the median CD4+ count, plasma HIV-1 RNA, number with PI resistance, and follow-up time were 340 cells/μL, 3.5 $\log_{10}$ copies/mL, 40 of 47 subjects, and 13.2 months, respectively. The median proportion of CD8+ cells that were CD38+/HLA-DR+ was 18.6% (range, 5%-50%). Repeated Measures Regression outcome modeling demonstrated that CD4+ cell change was a function of time and baseline proportion CD38+/HLA-DR+ CD8+ with decreases in CD4+ counts over time associated with higher proportions of CD38+/HLA-DR+ CD8+.

In a related presentation (Abstract 453), Karlsson and colleagues evaluated subjects with stable on-treatment plasma HIV-1 RNA values as follows: suppressed below 50 copies/mL (n = 13), suppressed but with episodes of non-sustained viremia ("blips"; n = 15), or sustained viremia in the range 50 to 1000 copies/mL (n = 18). HIV-specific T-cell immunity was measured using interferon (IFN)-gamma ELISPOT assay. T-cell activation was defined by CD38+ and HLA-DR coexpression. The median CD4+ count in the 3 groups was 674 cells/μL, 496 cells/μL, and 460 cells/μL, respectively. The median duration of this stable plasma HIV-1 RNA pattern preentry was 30 months, and subjects had a median of 27 months' follow-up on study. More than 50% of those with plasma HIV-1 RNA in the range of 50 copies/mL to 1000 copies/mL had HIV-1 RNA values above 1,000 copies/mL at 30 months. This was significantly shorter than the other 2 groups, where such failure was rare. Further the levels of HIV-specific T-cell immunity and T-cell activation were greater in breadth and magnitude in subjects with either intermittent or persistent low-level viremia compared with subjects with sustained viral suppression. Also those with persistent low-level viremia had increases in immune activation relative to those with blips. This group also had significant increases in PI ($P = 0.004$) and nRTI ($P = 0.005$) resistance over time. These data highlight negative aspects of persistent viremia in the range 50 copies/mL to 1,000 copies/mL relative to sustained suppression or blips. The authors suggested that therapy modification in the setting of stable viremia in the range 50 to 1000 copies/mL merits consideration.

Kieffer and colleagues (Abstracts 650, 651) reported the results of 2 studies evaluating genotypic evidence of resistance in those with stably suppressed plasma viremia. Abstract 651 was a study of plasma HIV-1 RNA estimates performed 3 times weekly for 12 weeks in 10 subjects with stable on-treatment suppression of the plasma HIV-1 RNA below 50 copies/mL for at least 6 months. Viral loads were run concurrently in 2 laboratories with the Roche Amplicor Monitor (1.5). So-called blips were observed in 9 of 10 subjects (mean, 2 blips/patient over 12 weeks). Only 2 blips lasted more than 96 hours. Defining a blip as a value above 150 HIV-1 RNA copies/mL, any quantifiable

value that was positive from both laboratories, or consecutive quantifiable values reduced the total number of blips from 20 to 4, and these were observed in only 2 patients. Clonal analysis of the plasma HIV reverse transcriptase was successful in 9 of 10 subjects with an average of 3 clones per patient at each time point. Resistance mutations were observed in 8 of 9 subjects at baseline but no evolution of resistance was observed. The authors contended that blips are common but often nonreproducible and not necessarily associated with evolution of preexisting drug resistance.

Fitness and Replication Capacity

Barbour (Abstract 388) described the HIV RCs in 191 recently infected antiretroviral-naive individuals. Using genotyping, 168 isolates were wild-type, 7 were PI resistant, 13 were only-nRTI resistant, 11 were only-NNRTI resistant, and 4 were only-nRTI and NNRTI resistant. Partial correlation coefficients of these resistant groupings (PI, nRTI, and NNRTI) to RC were 3.6%, 0.5%, and 1.7%, respectively, suggesting that the contributions of resistance motifs to RC were relatively modest. Isolates with PI mutations had significantly lower average RCs than wild-type isolates ($P = 0.01$). Split-regression analyses showed that isolates with RCs below 43% had higher CD4+ counts ($P = 0.004$). Further, a nonsignificant trend was observed such that on suppressive therapy for 18 months those with RCs below 43% averaged greater CD4+ count gains compared with those without.

Koh and colleagues (Abstract 634) evaluated the relative growth impact of specific *gag* cleavage site mutations E12K, L75R, H219Q, V390D, R409K, and L449F, and protease mutations L10F, V32I, M46I, I54M, A71V, and I84V derived by serial passage with amprenavir. A clone bearing only the PI mutations failed to replicate. Clones bearing combinations of these *gag* mutations replicated equivalently to wild-type clones and were as susceptible to amprenavir. Further, isolates bearing only these *gag* mutations passaged in the presence of amprenavir acquired amprenavir resistance mutations more rapidly than the wild-type virus. Thus *gag* mutations may impair replication but may also impact pathways to PI resistance.

Hu (Abstract 638) described the relative fitness patterns of site-directed mutants bearing the reverse transcriptase mutations T215F/Y in backgrounds of M41L, M41L/L210W, and M41L/D67N/L210W in the presence and absence of zidovudine. In all matched backgrounds the T215F recombinants replicated less efficiently than the T215Y mutant. The authors suggested these observations may explain the more frequent observation of the T215Y clusters.

Using data derived from drug-sensitive HIV-1 in the ViroLogic commercial database, Bates and colleagues evaluated associations between changes in the C-terminal 83 codons of HIV *gag* and differences in replication capacities (Abstract 121). Observed changes included lower replication capacities in isolates with mutations at codon 484 ($P = 0.0019$) and higher replication capacities in isolates with mutations 418 and those with insertions at codon 458—the so-called PTAPP motif. The authors speculated that such insertions at codon 458 may increase the efficacy of p6-Tsg101 binding, resulting in enhanced budding and higher replication capacity.

Resistance Associations by Genotype Database Analyses

Using data from 4907 genotypes at a commercial database, Flandre selected those with TAMs, or E44D and V118I exclusively, and evaluated mutations clustering by number of mutations (Abstract 645). Significant clustering of M41L/L210W/T215Y and D67N/K70R/T215F/K219E/Q was observed, with the former predominating when more than 3 mutations were present. Resistance to zidovudine and stavudine was also greater with the M41L/L210W/T215Y cluster. The most common single mutations were M41L, K70R, V118I, and T215Y, with the greatest level of resistance associated with the T215Y mutation.

Kagan employed a variety of statistical models to define associations between known resistance mutations and other changes in codons 1 to 400 of the HIV reverse transcriptase (Abstract 629). The 28,655 samples with genotypic resistance to a protease inhibitor or reverse transcriptase inhibitor were obtained between January 2002 and June 2003 and sequences stored at a commercial database. Three previously defined nRTI codon clusters (with associated novel codons) were observed as follows: previously defined, 41, 44, 118, 210, 215 (associated novel, 39, 43, 203, 223); 67, 69, 70, 219 (218, 228); and 62, 65, 68, 75, 77, 116, 151. Three previously defined NNRTI codon clusters (with associated novel codons) were observed as follows: 101, 108, 181, 190 (221); 106, 179, 188 (227); 100, 103, 225 (238).

International Studies on Resistance

HIV-2 strains are known to possess intrinsic resistance to FDA-approved NNRTIs. Reid described the nRTI resistance profiles of HIV-2 strains using primary isolates and reference strains with multiple cycle assays in MT4 cells (Abstract 691). Sequence homology between the various HIV-1 and HIV-2 strains tested was estimated at 64%. When HIV-2 strains were passaged with zidovudine selection of typical zidovudine mutations was observed uncommonly; when passaged in the presence of zidovudine/didanosine, few mutations were selected, including K65R, M184I, D67N, and H221Y. Phenotypic studies suggest a relatively greater intrinsic resistance of HIV-2 (compared with HIV-1) to zidovudine (ranging from 2.2- to >200-fold greater) but not to didanosine. Further, HIV-2 isolates had relatively efficient replication at high zidovudine concentrations.

Fleury and colleagues (Abstract 688) described the phylogenetic profiles of HIV isolates from antiretroviral-naive subjects at 2 international sites. In Abidjan, Cote D'Ivoire (n = 206), the relative subtype prevalence was CF02_AG > A > CRF06_cpx, CRF04_cpx. The protease polymorphism M36I was observed in 94% of CF02_AG samples. Mutations in HIV-1 associated with resistance were observed in 5.6% of samples. In Ho Chi Min city, Vietnam (n = 200), the CRF01_AE was the most predominant subtype. TAMS and the PI

mutations D30N and L90M were observed but rarely. Mutations associated with resistance in HIV-1 were observed in 6.5% of samples.

Hall and colleagues (Abstract 694) compared outcomes by clade B or C infection in the 1216 individuals enrolled in the 2NN study. This international study evaluated the 48-week outcomes in drug-naive individuals treated with distinct nevirapine- and efavirenz-based regimens, each in combination with stavudine and lamivudine. Comparison was made between 174 randomly chosen participants and 102 with virologic failure (ie, failure to reach or to sustain an HIV-1 RNA below 50 copies/mL). More virologic failures than randomly selected patients were subtype C, with 48% and 36%, respectively. Also more of the virologic failures were from South Africa than the randomly selected patients: 56% and 36%, respectively. Treatment emergent mutations K103N and V106M were more common in those with subtype C or on efavirenz. Among those with baseline resistance, 12 of 13 experienced virologic failure. Notably, K65R was observed in 8 of 119 subjects whose nRTI therapy was stavudine/lamivudine, supporting recent observations that this mutation can emerge on stavudine-based therapy.

A presentation by Aluoch (Abstract 580) noted a failure to define any known resistance mutations in 34 HIV-1 subtype C isolates from 34 treatment naive individuals in South Africa. Some polymorphisms were seen more frequently in subtype C than subtype B HIV-1, including E36A (72% vs 0%, respectively), T39E/D (93% vs 0%), K173A/T (100% vs 0%), and in protease L89I/M (97% vs 0%).

A complementary presentation by Calazans (Abstract 692) suggested that the L89M change in subtype F protease may impact resistance to PIs. L89M site-directed mutants were constructed using protease-susceptible clones of subtype B and F. By MT4 cell-MTT cell viability assay, the L89M mutation conferred 6.2-, 5.6-, 4.7-, 4.5-, 3.4-, and 2.0-fold increases in EC_{50} to nelfinavir, indinavir, ritonavir, amprenavir, lopinavir and saquinavir, respectively. The clinical relevance of these changes with respect to treatment failure with non-clade B strains merits further evaluation.

Torimiro and colleagues (Abstract 223) evaluated HIV diversity among 41 HIV seropositive rural rainforest dwellers in Cameroon. The prevalence of HIV was 3.1%. Phylogenetic classification of protease-RT sequences showed that 95% were recombinants, with many novel strains. Limited full-length sequencing of 11 isolates showed that most contained partial sequences from subtypes A and E. The ongoing evolution of this locally mature epidemic has relevance to regions where the epidemic is more recent and for vaccine strategies.

Petroni and colleagues (Abstract 693) evaluated the prevalence of HIV recombinants among 316 Argentinean individuals whose samples were evaluated at a reference laboratory between June 1999 and February 2002. Cross-sample phylogenetic comparisons were made of the HIV protease and the first 960 bases of the RT. The observed distribution of subtypes was B 51.9%, B/F recombinant 47.8%, and F 0.3%. The B/F recombinant was significantly more common among women ($P = < 0.001$) and children ($P = < 0.001$). Among isolates with protease mutations at codons V82A/F/T, the changes K20R/M and I54V/L were observed more frequently among B/F recombinants.

Pharmacology

nRTI

Gries and colleagues presented substudy results from a randomized clinical trial of ribavirin and either pegylated interferon alfa-2a or interferon alfa-2a in the management of hepatitis C virus infection in HIV-infected patients (Abstract 136). They examined the intracellular and plasma pharmacokinetics of zidovudine, lamivudine, and stavudine in patients before and after receiving ribavirin and peginterferon alfa-2a for 8 to 12 weeks. The plasma $AUC_{0\text{-}12hr}$ of zidovudine, lamivudine, and stavudine were not altered after the addition of ribavirin and peginterferon alfa-2a, nor were the intracellular AUC0-12hr values of their active triphosphorlyated forms.

Kearney and colleagues investigated the pharmacokinetics of tenofovir in patients with hepatic impairment and in patients receiving therapy for viral hepatitis (Abstract 600). Tenofovir pharmacokinetics were similar among patients with severe hepatic impairment (n = 8), moderate impairment (n = 7), and unimpaired controls (n = 8) as defined by the Child-Pugh-Turcotte system. They also examined the single-dose pharmacokinetics of adefovir and ribavirin with and without tenofovir, and found no significant interactions.

Kaul and colleagues evaluated the pharmacokinetics of extended-release stavudine with and without tenofovir in 18 HIV-seronegative subjects (Abstract 602). They did not find a significant change in the C_{max}, AUC, or median time to maximal concentration in stavudine when coadministered with tenofovir.

Efavirenz

Taylor and colleagues evaluated efavirenz concentrations in 8 patients for 3 weeks after discontinuation of the drug (Abstract 131). The indication for stopping efavirenz included virologic failure, toxicity, change of dual NNRTI to single nRTI, or treatment interruption after seroconversion. They also evaluated 25 other patients who were interrupting antiretroviral therapy post seroconversion and stopped efavirenz 5 to 7 days prior to stopping nRTIs. They found significant plasma levels of efavirenz 2 weeks after discontinuation. Although they did not detect any new resistance mutations in patients stopping efavirenz 7 days prior to stopping nRTIs, they concluded that efavirenz should be discontinued 2 weeks prior to stopping nRTIs, or that it should be exchanged for another antiretroviral medication with a shorter half-life prior to interrupting therapy.

Ribaudo and colleagues presented data on efavirenz pharmacokinetics from a substudy of ACTG 5095 (Abstract 132). They found that race was significantly related to clearance of efavirenz: white, non-Hispanic subjects had a 32% faster clearance than black or Hispanic subjects. There was also some evidence that drug discontinuation was related to decreased clearance ($P = 0.052$) and increased C_{max} ($P = 0.048$). These parameters were not related to virologic response or rates of a first central nervous system toxicity. Authors from the same study, Haas and colleagues,

offered an explanation for this differential rate of clearance (Abstract 133). They linked decreased clearance of efavirenz to a common allelic variant at CYP2B6, the enzyme mainly responsible for metabolizing efavirenz. The variant was more common among blacks (20%) than whites (3%) and was associated with a 3-fold-higher plasma efavirenz level.

Hitti and colleagues examined the association of sex and weight with the pharmacokinetics of efavirenz, indinavir, and nelfinavir with data collected from 6 different ACTG trials (Abstract 604). They found no association of sex with nelfinavir, M8 (an active metabolite of nelfinavir), or indinavir levels. However, they found a significantly lower efavirenz AUC in women compared with men. This is in contrast to the study by Ribaudo, which did not find an association between sex and efavirenz AUC. They also examined the association of weight with the pharmacokinetics of these drugs. Increased weight reduced the AUC of efavirenz and indinavir.

Gerber and colleagues presented the results of ACTG 5108, which evaluated the effect of efavirenz on simvistatin and atorvastatin levels in 27 HIV-seronegative individuals (Abstract 603). Efavirenz reduced the AUC_{24} of simvistatin by 58%, and atorvastatin by 43%. This suggests that higher doses of simvistatin and atorvastatin may be necessary to achieve the desired effects on plasma lipid levels.

Drug-Drug Interactions

Triple protease inhibitors. Boffito and colleagues presented data on the pharmacokinetics of saquinavir (hard gel formulation) administered with low-dose ritonavir, and given with and without atazanavir (Abstract 607). Saquinavir 1600 mg was given with ritonavir 100 mg for 1 dose to 20 HIV-infected participants. On day 2, the same doses were continued each day along with atazanavir 300 mg qd for 30 days. There were no discernable changes in plasma lipids after addition of atazanavir. There was a significant increase in plasma bilirubin levels. They found that administration of atazanavir increased the C_{trough}, C_{max}, and AUC by 60%, 42% and 112%, respectively. The authors postulated that atazanavir may boost saquinavir levels by a mechanism distinct from that of ritonavir.

ACTG 5143 showed a significant decrease in both lopinavir and amprenavir levels when fosamprenavir and lopinavir/ritonavir were administered together. Corbett and colleagues presented the results of 2 strategies to overcome this interaction, neither of which were satisfactory (Abstract 611). Eleven HIV-seronegative subjects received lopinavir 400 mg/ritonavir 100 mg plus 700 mg of fosamprenavir bid for 7 days. Then they received the same doses separated by 4 hours for 7 days. After this, they received lopinavir 800 mg/ritonavir 200 mg qd and fosamprenavir 1400 mg qd separated by 12 hours. Compared with simultaneous administration, the 2 separation strategies resulted in significantly higher lopinavir levels, but amprenavir levels remained suboptimal.

A second study presented by Wire and colleagues also evaluated the interaction of fosamprenavir and lopinavir/ritonavir (Abstract 612). They tried 2 dosing strategies to improve drug levels of amprenavir and lopinavir. 36 subjects received lopinavir 400 mg/ritonavir 100 mg bid or amprenavir 600 mg/ritonavir 100 mg bid as the control treatment. In the first study, subjects received fosamprenavir 1400 mg bid plus lopinavir 533 mg/ritonavir 133 mg. Thirteen of 36 subjects dropped out early, mostly due to side effects. In the second study, subjects received lopinavir 400 mg bid/ritonavir 200 mg bid, and fosamprenavir 700 mg bid. Sixteen of 36 dropped out early, mostly due to side effects. Both studies resulted in lopinavir levels that were higher than when subjects received lopinavir/ritonavir alone. However, amprenavir levels were significantly reduced in both studies compared with receiving fosamprenavir/ritonavir alone. The authors concluded that the suboptimal amprenavir levels coupled with the high rate of side effects limited the utility of these dosing strategies.

Vezina and colleagues followed up 12 HIV-infected subjects on lopinavir 400 mg/ritonavir 100 mg bid along with amprenavir 600 mg bid (Abstract 609). After 2 weeks, pharmacokinetic sampling was performed. Dose adjustments were made to assure drug levels consistent with manufacturer's recommendations. Six of 12 patients required increased doses of lopinavir/ritonavir (2 received 533 mg/133 mg and 4 received 667 mg/167 mg). Three of 12 participants required an increase of amprenavir (2 received 750 mg and 1 received 900 mg). No adverse events were noted. The authors concluded that the interaction between these drugs was difficult to predict and dose individualization through pharmacokinetic monitoring may be indicated.

Tenofovir/didanosine. Dose reduction for didanosine when co-administered with tenofovir has previously been recommended due to increased didanosine levels in the presence of tenofovir and an increased rate of pancreatitis. Clotet and colleagues (Abstract 749) raised concerns for a potential toxicity associated with combination tenofovir and full-dose didanosine (400 mg qd). In a retrospective database analysis, 150 subjects with plasma HIV-1 RNA below 50 copies/mL switching to tenofovir/didanosine were compared with a similar group of 152 subjects switching to either full-dose didanosine or tenofovir. After changing therapy, subjects maintained suppression of plasma HIV-1 RNA. More than 50% of subjects in the tenofovir/didanosine group had reductions of more than 100 CD4+ cells/μL, and up to 30% of this group lost more than 200 cells/μL, at last follow-up ($P \leq 0.05$). By comparison, 85% to 90% of subjects in the tenofovir or didanosine groups, respectively, had CD4+ counts that were unchanged or had increased. Eight subjects on tenofovir/didanosine underwent a didanosine dose reduction to 250 mg/day; 3 months after this the mean increase in CD4+ count was 60 cells/μL. The authors raised concerns for a potential toxicity associated with full-dose didanosine in combination with tenofovir.

Lopinavir and saquinavir. Dam evaluated the in vitro antiviral activity of a variety of fixed-molar combinations of lopinavir and saquinavir against wild-type and mutant HIV strains in a single-cycle cell-indicator assay (Abstract 622). Enhancement of saquinavir activity by

lopinavir was observed in isolates with low-level saquinavir resistance but high-level lopinavir resistance ($P = 0.0004$). Contrary to prior reports, synergism was not observed with wild-type isolates.

Mother-To-Child Transmission of HIV

Single-dose nevirapine has gained acceptance as a simple, inexpensive, and effective intervention to decrease mother-to-child transmission (MTCT) of HIV. Previous studies have documented a high rate of NNRTI-resistant virus in mothers in the immediate post-partum period. Access to antiretroviral therapy in the developing world is growing, and NNRTI-based regimens will likely be used often. The impact of NNRTI resistance on these women's future responses to NNRTI-based therapy has not previously been reported.

Martinson and colleagues presented a large study of 623 South African women receiving single-dose nevirapine for prevention of MTCT (Abstract 39). Overall, 38.2% of women and 42.4% of their infants had NNRTI resistance in the postpartum period. The rate of MTCT was 8.6%. Nevirapine resistance was associated with MTCT in a univariate analysis, but this was not evident after controlling for maternal viral load and CD4+ cell count. Nevirapine resistance in the mother was related to lower CD4+ cell counts, higher plasma HIV RNA levels, shorter time from delivery to genotypic testing, and receiving more than 1 dose of nevirapine prior to delivery (women received extra doses of nevirapine in some cases, eg, for false labor or extremely prolonged labor).

Lallemant and colleagues evaluated single-dose nevirapine in combination with zidovudine for prevention of MTCT (Abstract 40). All women in this randomized, double-blind, placebo-controlled trial received open-label zidovudine starting in the third trimester. The women were randomized to receive either nevirapine at delivery, and nevirapine for the infant, nevirapine at delivery and placebo for the infant, or placebo at delivery and placebo for the infant. The placebo-placebo arm was discontinued after the first interim analysis. At that time, the MTCT rate for placebo-placebo was 6.3% (95% confidence interval [CI], 4.2-9.5%) compared with 1.1% (95% CI, 0.4-3.0%) for nevirapine-nevirapine. The final results for the nevirapine-nevirapine and nevirapine-placebo arms were 2.0% (95% CI, 1.2-3.4%) and 2.8% (95% CI, 1.8-4.4%), respectively, which met the protocol definition for noninferiority.

Chalermchokcharoenkit and colleagues presented results from an open-label study of 220 HIV-infected pregnant women who were given zidovudine starting at 34 to 36 weeks, followed by an intrapartum single dose of nevirapine (Abstract 96). Infants were given a single dose of nevirapine and 2 weeks of zidovudine after birth. They found that 10 of 223 infants (4.6%; 95% CI, 2.5%-8.6%) became HIV-infected, and 5 of 10 were HIV RNA PCR-positive at birth. One month postpartum, 17% and 2% of women had nevirapine and zidovudine resistance, respectively. Two of 10 HIV-infected infants had nevirapine resistance. This regimen was well tolerated, and anemia was the most common adverse event.

Jourdain and colleagues presented the results of an open-label study of 255 women starting a first nevirapine-based antiretroviral regimen (Abstract 41). Forty-two were not previously exposed to nevirapine, and 213 had received single-dose nevirapine during pregnancy to prevent MTCT. Sixty-three of 213 women exposed to nevirapine were previously found to have had genotypes associated with NNRTI resistance from samples obtained 2 weeks postpartum. The median baseline CD4+ counts were 169 cells/μL and 182 cells/μL in the nevirapine-exposed and unexposed groups, respectively, and the mean plasma HIV-1 RNAs were 4.61 $\log_{10}$ copies/mL and 4.51 $\log_{10}$ copies/mL, respectively. In the nevirapine-unexposed group, 75% had fewer than 50 HIV-1 RNA copies/mL 6 months after starting the nevirapine-based regimen, compared with 53% of the nevirapine-exposed women who did not have genotypic evidence of resistance postpartum and 34% of the nevirapine-exposed women who did have genotypic evidence of resistance. This implies women receiving single-dose nevirapine have an increased rate of virologic failure during subsequent NNRTI-based regimens.

Shapiro and colleagues presented results on behalf of the PACTG regarding mode of delivery and risk of MTCT (Abstract 99). They focused their analysis on the role of elective caesarian section in women who had plasma HIV RNA levels below 1000 copies/mL. The overall risk of MTCT was 0.7% in this group. After controlling for known risk factors for MTCT (plasma HIV RNA levels, use of multidrug antiretroviral therapy, maternal CD4+ cell count, etc), they did not find a benefit of elective caesarian section, but did find a benefit of multidrug antiretroviral therapy even when having such a low plasma HIV RNA.

International Studies

South Africa

Churchyard and colleagues summarized an antiretroviral therapy program for gold miners in South Africa (Abstract 2). The prevalence of HIV infection in this population is estimated at 28%. The gold-mining company began a program in August 2002 to provide antiretroviral medications for those in need via a comprehensive, standardized delivery system. The first-line regimen was zidovudine/lamivudine/efavirenz, and the second-line regimen was didanosine/abacavir/lopinavir/ritonavir.

Overall, 1222 employees were eligible for antiretroviral therapy and 1098 (90%) started therapy. In 305 (28%), adverse events occurred, including 17 (1.6%) grade 4 events. There were 37 (3.4%) deaths after starting antiretroviral therapy. Retention was excellent, with 92% remaining in the antiretroviral therapy program. The median baseline CD4+ count was 145 cells/μL, and this nearly doubled 6 months after starting antiretroviral therapy. At 6 months, 60% had an HIV RNA level below 50 copies/mL. Interestingly, participation of gold miners in the voluntary counseling and testing program increased significantly during the same time period, highlighting the link between access to antiretroviral therapy and willingness to be tested for HIV.

Mozambique

Palombi and colleagues presented the results of the DREAM Project, which has enrolled 802 adults (including 510

women) and 215 children since February 2002 (Abstract 148). Approximately one-half of adults and one-third of children have started antiretroviral therapy (zidovudine or stavudine, plus lamivudine and nevirapine). The lost-to-follow-up rate was 9.3% in adults and 3.3% in children. The proportion of adults with a CD4+ count below 200 cells/µL decreased from 68.2% at baseline to 22.4% after 1 year of antiretroviral therapy. Approximately 75% achieved and maintained an HIV RNA level below 50 copies/mL at 1 year. Among the children, the median decline in HIV RNA was 5.2 $\log_{10}$ copies/mL and the CD4+ cell percentage increased by a median of 10.4 percentage points. The death rate was 12.5% and 11.5% in adults and children, respectively.

India

Patel and colleagues presented results from a clinical cohort from Ahmedabad and Pune, India (Abstract 584). They compared the CD4+ cell count responses to efavirenz- (n = 254) or nevirapine- (n = 254) based regimens. The median baseline CD4+ counts were 100 cells/µL and 115 cells/µL, respectively. The median CD4+ counts after 1 year of starting antiretroviral therapy increased by 259 cells/µL and 213 cells/µL, respectively. The authors commented that these results compared favorably to the results of the 2NN study. For comparison, the median CD4+ count in the efavirenz and nevirapine (bid) arms of the 2NN study were 190 cells/µL and 180 cells/µL, respectively, and the average CD4+ count rises at 48 weeks were 160 and 160 cells/µL, respectively (van Leth et al, 10th CROI, 2003).

Thailand

Sungkanuparph and colleagues presented the results of an analysis of 159 patients starting antiretroviral therapy with CD4+ counts below 50 cells/µL in a clinical cohort (Abstract 587). The median baseline CD4+ count was 22 cells/µL, and the median baseline HIV-1 RNA was 260,000 copies/mL. There were 14 patients who discontinued antiretroviral therapy due to adverse events, 5 who were lost to follow-up, and 2 who died. Of those remaining on antiretroviral therapy, the median CD4+ count rise at 1 year was 201 cells/µL, and the percent with HIV RNA levels below 400 copies/mL (and < 50 copies/mL) was 91% (and 79%).

Conclusions

In 2004 the CROI maintained its position as the preeminent research conference of the year, presenting state-of-the-art information, including that concerning advances in antiretroviral therapy. New drugs on the horizon, updated knowledge on how to better use available drugs, the implications of viral resistance, and the internationalization of antiretroviral therapeutics presented a picture of cautious hope for continued improvements in care for HIV-infected individuals worldwide.

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Conference Abstracts cited in text can be found at www.retroconference.org.

Additional Suggested Readings

Cahn P, Lange J, Cassetti I. Anti HIV-1 activity of SPD754 a new NRTI: results of a 10 day monotherapy study in treatment naive HIV patients. [Abstract LB15.] 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment. July 13-16, 2003; Paris, France.

Derdeyn CA, Decker JM, Bibollet-Ruche F, et al. Selective Heterosexual Transmission of Envelope-constrained, Neutralization-sensitive HIV-1 [Abstract 127]. 10th Conference on Retrovirus and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

Van Leth F, Hassink E, Phanuphak P, et al. Results of the 2NN study: A randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine. [Abstract 176.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

Complications of HIV Disease and Antiretroviral Therapy

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

This year's conference provided newer insights on the complications of antiretroviral therapy, as well as into the complications that arise from HIV infection itself. Many presentations at the conference centered around metabolic complications of therapy, including lipid abnormalities, diabetes, body composition changes, bone disorders, and cardiovascular disease. New data on complications of HIV infection itself were presented, including those on coinfections with hepatitis B, C, and herpes simplex viruses, malaria, and tuberculosis, as well as complications that are important during pregnancy. This article summarizes these presentations.

Metabolic Complications

Metabolic complications continue to play a major role in the management of HIV infection. This year's conference featured more than 50 abstracts describing research directed toward understanding the pathogenesis, treatment, and long-term consequences of metabolic abnormalities associated with HIV infection and the use of antiretroviral therapy. This section is divided into sections about the pathogenesis of metabolic complications, lipid abnormalities, diabetes, lipoatrophy and lipohypertrophy, bone disorders, and cardiovascular disease.

Pathogenesis of Metabolic Complications

In vitro studies have suggested that protease inhibitors (PIs) may influence lipid metabolism by interfering with the degradation by proteasomes in hepatocytes and adipocytes, thus influencing the expression of genes involved in lipid metabolism. Specific PIs differ in their lipid effects in vitro. Most earlier studies have shown conflicting results with respect to lipid effects in vitro and in vivo. Parker and colleagues compared the effects of lopinavir, ritonavir, nelfinavir, and atazanavir on gene expression in vitro in hepatocyte and adipocyte cell lines (Abstract 706). Using drug concentrations designed to mimic those observed in vivo, they measured induction and inhibition of gene expression each qualitatively and quantitatively. Lopinavir, ritonavir, and nelfinavir each had a greater impact on induction of genes involved in lipid metabolism than did atazanavir in both cell lines. In addition, it appeared that genes involved in lipid synthesis were also upregulated in hepatocytes by lopinavir, ritonavir, and nelfinavir, but repressed in adipocytes, consistent with the observations in vivo of increased hepatic lipid synthesis but reduced storage in fat cells. These investigators proposed that inhibition of proteasomes in vivo with the resultant impact on lipid biosynthesis may be the etiology of PI-associated dyslipidemia, and the absence of an effect of atazanavir on these pathways may explain the absence of dyslipidemia seen with this drug in vitro. Further clinical studies are needed to determine whether the absence of lipid effects of atazanavir translates into a reduced impact on body composition over time.

Previous studies have suggested that insulin resistance may be associated with drugs in the PI class. In vitro and clinical studies suggest PIs may vary in their propensity to cause insulin resistance. For example, atazanavir—unlike indinavir, lopinavir, and ritonavir—does not appear to block the glucose transporter GLUT 4 in vivo. Noor and colleagues at Bristol-Myers Squibb, with collaborators at University of California San Francisco, conducted a randomized, double-blind, placebo-controlled trial with a 2 period crossover design to examine the impact of atazanavir and lopinavir/ritonavir (lopinavir/r) on insulin-stimulated glucose uptake in HIV-uninfected adults. This labor-intensive, hyperinsulinemic, euglycemic clamp study is considered the gold standard for determining the presence of insulin resistance. Subjects were randomized to receive standard doses of atazanavir (400 mg/d), lopinavir/r (400 mg/100 mg twice daily), or placebo. Following 5 days of treatment, the clamp procedure was performed to determine the rate of glucose disposal at steady state following a continuous infusion of insulin. Mean values of insulin-stimulated glucose disposal (M/I) did not vary between atazanavir and placebo; however, the difference between lopinavir/r plus atazanavir and lopinavir/r plus placebo was statistically significant, suggesting that lopinavir/r, but not atazanavir, had an unfavorable impact on glucose metabolism.

Atazanavir also had no impact on measures of insulin sensitivity; however, a statistically significant decrease in insulin sensitivity was observed with lopinavir/r. The results of this well-designed and carefully conducted study suggest that lopinavir/r has acute effects detected by a sensitive measure of glucose metabolism in non-HIV-infected adults. Previous studies in a smaller number of non-HIV-infected volunteers using this same euglycemic, hyperinsulinemic clamp method demonstrated that 4 weeks of treatment with indinavir was associated with the development of insulin resistance, whereas lopinavir/r treatment had no effect on insulin sensitivity (Abstract

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705). It is not clear whether the difference in results between these studies is perhaps due to the shorter treatment period (5 days) or the larger sample size of the most recent study. The impact of these findings on long-term outcomes of HIV-infected patients taking these drugs merits close attention.

Lipid and glucose metabolism kinetics were also examined in HIV-infected subjects who had evidence of metabolic complications (ie, body fat maldistribution assessed by dual-energy x-ray absorptiometry scanning [DEXA], triglyceride level > 200 mg/dL, or impaired glucose tolerance) and were compared with a control group of HIV-infected subjects who did not have such evidence of metabolic complications (Abstract 703). Glucose and lipid disposal were examined using a euglycemic, hyperinsulinemic clamp technique and stable isotope tracers. The subjects with HIV-related metabolic complications had marked impairment of insulin-mediated suppression of lipolysis and glucose production, and a reduction in the ability of insulin to promote glucose disposal. These findings led the investigators to conclude that increased mobilization of lipid stores may contribute to the dyslipidemia and changes in body composition observed in HIV infection.

There is also great interest in the role of adiponectin, a hormone secreted by adipocytes, in the pathogenesis of body composition changes observed during treatment of HIV infection. Cross-sectional studies have demonstrated reduced circulating levels of adiponectin in patients with both lipoatrophy and lipohypertrophy. In addition, reduced levels of adiponectin have been correlated with the presence of insulin resistance. Lee and colleagues assayed samples collected during their previously reported clamp studies of indinavir and lopinavir/r and found that adiponectin levels were increased following exposure to both of these drugs, and this increase in adiponectin appeared to be independent of insulin resistance (Abstract 705). Jones and colleagues examined adiponectin and tumor necrosis factor (TNF) expression from adipocytes obtained from HIV-infected subjects undergoing surgical procedures (Abstract 707). Adipocytes were obtained from subcutaneous and omental fat depots, and the cells were later exposed to a variety of antiretroviral drugs in vitro. Adiponectin expression was higher in subcutaneous than in omental fat cells in these drug-naive subjects, and adiponectin messenger RNA (mRNA) expression appeared to be inversely related to TNF mRNA expression. PIs (with the exception of atazanavir) and nucleoside reverse transcriptase inhibitors ([nRTIs]; zidovudine and stavudine) significantly decreased adiponectin expression in adipocytes obtained from the subcutaneous depots, suggesting a mechanism by which these drugs might lead to the development of insulin resistance and lipoatrophy. Prospective studies of antiretroviral-naive patients taking on different antiretroviral regimens are needed to determine the relationship between early effects drug exposure on insulin resistance and adiponectin levels, both in adipose tissue and in the circulation, and the subsequent development of lipoatrophy or lipohypertrophy.

The nRTIs have been implicated in the pathogenesis of lipoatrophy. Most of the previous work in this area focused on the impact of nRTIs on mitochondrial DNA content in peripheral blood mononuclear cells (PBMCs), and more recently in fat biopsies. At this year's conference, several groups extended our understanding of this important area of research. Casula and colleagues reported longitudinal data on levels of mitochondrial DNA (mtDNA) and RNA content from PBMCs collected in a randomized clinical trial comparing a regimen containing indinavir with a regimen containing efavirenz, each with or without stavudine (Abstract 709). Following 48 weeks of antiretroviral treatment, levels of mtDNA and mtRNA increased above baseline in both groups, and there was no statistically significant difference between the treatment arms. These results suggest that PBMCs may not be the cells to assess mitochondrial toxicity. A cross-sectional study (Abstract 710) in which lipoatrophic HIV-infected patients had reduced levels of mtDNA in adipose tissue but not in PBMCs reached this same conclusion and also suggested that fat tissue may be the best tissue to examine the impact of nRTI treatment. McComsey examined markers of mitochondrial function from skeletal muscle samples from subjects who had participated in a trial replacing stavudine with abacavir or zidovudine. This trial had previously demonstrated improvements in lipoatrophy following the nRTI switch. Despite this clinical improvement, only a partial improvement in mitochondrial function was seen at 48 weeks, suggesting that the mtDNA depletion may not be the sole mechanism involved in mitochondrial dysfunction. Finally, Mallon and collaborators reported the results of an elegant study of the impact of short-term nRTI therapy in HIV-uninfected volunteers (Abstract 76). In this randomized trial, 20 subjects received either stavudine/lamivudine or zidovudine/lamivudine for 6 weeks, followed by a washout period. Adipose tissue biopsies were obtained from the flank region at baseline and at week 2 and studies were conducted to examine the impact of the nRTIs on mitochondrial and nuclear genes. Mitochondrial and peroxisome proliferator-activated receptor-γ (PPAR–γ) gene expression decreased significantly at week 2 in both groups, but sterol regulatory binding protein 1 (SREBP1) was not affected. These early changes in mitochondrial and nuclear gene expression predated any changes in fat mass in the study subjects. These results suggest that combination nRTI therapy may have a direct effect on expression of metabolism genes (both mitochondrial and nuclear genes) in adipocytes in the absence of HIV infection, and these changes could contribute alone or in combination with PIs to the pathogenesis of lipoatrophy over time.

Lipids

Several groups reported on the prevalence and risk factors for dyslipidemia within ongoing cohorts and controlled clinical trials (Abstracts 74, 712–717). Investigators in the Community Programs for Clinical Research on AIDS (CPCRA) examined risk factors for low levels of high-density lipoprotein cholesterol (HDL-c) in a cross-sectional analysis of 1028 subjects enrolled in

the ongoing Strategies for Anti-Retroviral Therapy (SMART) study (Abstract 712). Nearly half (44.5%) of the cohort had a baseline HDL-c level of less than 40 mg/dL. As expected, low HDL-c was more common among those not on antiretroviral therapy, and it appeared to be associated with higher values of HIV RNA. Among those on antiretroviral therapy, use of an nonnucleoside reverse transcriptase inhibitor (NNRTI) was associated with higher HDL-c, and traditional risk factors were associated with low HDL-c. In a multivariate model of risk factors for low HDL-c among those on treatment, younger, age, female sex, black race, and NNRTI-containing antiretroviral therapy regimens were protective against low HDL-c, and diabetes and triglyceride levels above 200 mg/dL increased the risk of low HDL-c. Among those on NNRTI plus nRTI-based antiretroviral therapy, the presence of 3 or more traditional risk factors increased the prevalence of low HDL-c from 15.7% for those with no risk factors to 45% for those with 3 or more risk factors. These results suggest that traditional risk factors and type of antiretroviral therapy are both important determinants of low HDL-c in HIV infection.

The metabolic substudy (A5005s) of the large randomized controlled AIDS Clinical Trials Group (ACTG) 384 trial was designed to determine whether nelfinavir- and efavirenz-based therapies differ with respect to changes in lipid and insulin levels (Abstract 74). The study also compared the impact of the nRTI-backbone regimens in the trial (zidovudine/lamivudine vs didanosine/stavudine) on metabolic parameters. Increases in total cholesterol levels were similar in the efavirenz and nelfinavir groups, and increases in HDL-c were more common in the efavirenz-treated patients, yielding a more favorable total cholesterol-to-HDL-c ratio in the efavirenz group. Neither treatment assignment was associated with large increases in triglyceride levels: Only 6% of efavirenz and 5% of nelfinavir recipients experienced triglyceride increases above 400 mg/dL at 32 weeks. Zidovudine/lamivudine treatment was associated with more favorable lipid parameters than didanosine/stavudine. Insulin resistance appeared to worsen in the group over time, with no differences noted between treatment groups.

Powderly and colleagues compared lipid values and body shape changes among subjects randomized to receive efavirenz and didanosine-EC (enteric coated) combined with either stavudine or emtricitabine over 72 weeks (Abstract 717). More favorable effects on triglyceride and HDL-c levels were seen among the emtricitabine/didanosine group compared with those who received stavudine/didanosine. In this trial, treatment with stavudine was also associated with greater decrease in body weight, body mass index, abdominal girth, waist circumference, and waist-to-hip ratio than was treatment with emtricitabine, consistent with the suspected role of stavudine in the development of lipoatrophy.

Elevated lipid levels, and in particular, increases in triglyceride levels, have been well described during treatment with the PI lopinavir/r. Almost all early data on lipids with lopinavir/r-based regimens came from studies that included the nRTI backbone of stavudine/lamivudine. Since stavudine use has been associated with increases in triglyceride levels in other trials (ie, Gilead 903, ESS4002 Study [Abstract 713]), it is of interest to examine prospective data on lipids among patients treated with lopinavir/r when combined with non-stavudine-containing nRTIs. Gathe and colleagues presented the results of a 48-week study that compared once-daily with twice-daily lopinavir/r plus tenofovir/emtricitabine (Abstract 570). Lipid changes were comparable in the once-daily and twice-daily lopinavir/r dosing arms, with modest (but statistically significant) increases in total cholesterol (27 mg/dL), HDL-c (3 mg/dL to 6 mg/dL), and low-density lipoprotein cholesterol ([LDL-c]; 13 mg/dL to 14 mg/dL). The mean change in total cholesterol level was smaller than the mean increase of about 53 mg/dL described in earlier trials with lopinavir/r. The mean change in triglyceride level was 82 mg/dL and 76 mg/dL in the once-daily and twice-daily dose groups, respectively, and this appears to be slightly less than the mean change of about 125 mg/dL change noted in early trials with lopinavir/r combined with stavudine/lamivudine. These results suggest that the use of a tenofovir/emtricitabine nRTI backbone might decrease, but might not eliminate, the hypertrigylceridemia that is observed among some patients who receive lopinavir/r-based therapy.

In another study of treatment-experienced patients, baseline triglyceride level was the best predictor of developing further increases in triglyceride level while on lopinavir/r (Abstract 714). Finally, comparative data from the MaxCmin trial demonstrated that triglyceride increases were evident (median increase, 29%) in subjects randomized to receive lopinavir/r, compared with no statistically significant change for those who received saquinavir/ritonavir (Abstract 720).

Treatment with lipid-lowering drugs in the setting of antiretroviral therapy has only been modestly successful. Aberg and ACTG colleagues reported follow-up data from a randomized trial comparing pravastatin and fenofibrate for the treatment of dyslipidemia in antiretroviral-therapy-treated subjects (Abstract 723). Subjects who did not reach the National Cholesterol Education Program (NCEP) goal for both triglyceride and LDL-c levels by week 12 on lipid-lowering monotherapy (>95% of study subjects) were offered combination fenofibrate/pravastatin therapy and were followed up for 48 weeks. The combination of fenofibrate/pravastatin was safe and well tolerated; however, few subjects met NCEP goals for cholesterol and triglyceride levels at the end of the study. For subjects with elevated triglyceride levels, treatment with fenofibrate alone followed by the combination pravastatin/fenofibrate appeared to offer the best response.

Statin therapy may have additional benefits beyond the impact on values of total cholesterol and LDL-c. This was evaluated in a small, double-blind, placebo-controlled trial of pravastatin in which lipoprotein subfractions and endothelial function were included as endpoints. Pravastatin treatment was associated with an 18% decrease in total cholesterol and a 20% decrease

in LDL-c. In addition, pravastatin was associated with reduced atherogenic lipid fractions, like small LDL-c and small very low density lipoprotein (VLDL) levels, and improved endothelial function as measured by flow mediated dilatation of the brachial artery.

Another option for lowering hypertrigylceridemia is the use omega-3 fatty acids or fish oil. Wohl and colleagues conducted an open-label study evaluating a diet and exercise intervention with or without the addition of 3 g of fish oil per day in non-diabetic HIV-infected subjects with elevated triglyceride levels on antiretroviral therapy. Although there was a transient benefit from fish oil at week 4, by the end of 4 months of treatment only modest decreases in triglyceride levels were noted, and no differences were seen between treatment arms. Whether higher doses of fish oil will offer clinically significant decreases in hypertrigylceridemia remains to be determined.

Given the modest impact of lipid-lowering drugs on dyslipidemia among patients on antiretroviral therapy, interest remains in strategies that include substituting the component of therapy that is the likely cause of the problem. One factor that may influence the ability of single-drug substitutions to improve dyslipidemia is the presence of lipoatrophy or lipohypertrophy at the time of the switch. Fisac presented follow-up results of the lipid substudy of the larger NEFA switch study called NEFA, in which either nevirapine, efavirenz, or abacavir was substituted for the PI component of a successful antiretroviral therapy regimen (Abstract 78). Two years following the switch to PI-sparing antiretroviral therapy, the earlier improvements in total cholesterol, HDL-c, and non-HDL-c levels appeared to be maintained in all treatment groups. Of note, triglyceride levels were statistically significantly reduced at 12 months but appeared to be on the rise by 24 months. Subjects with moderate to severe clinical lipodystrophy appeared to be less sensitive to the improvements in dyslipidemia seen with changing therapy. These results highlight the possible interrelationship between changes in body composition and dyslipidemia, and may also provide insights into why conventional lipid-lowering drugs have only modest effects.

Diabetes

There is a growing interest in the relationship between HIV infection, antiretroviral therapy, traditional risk factors for diabetes, and the prevalence and incidence of diabetes among HIV-infected subjects. Historical data on the risk of diabetes among men were reported from the Multicenter AIDS Cohort Study ([MACS]; Abstract 73). Prevalent diabetes was 4 times more common among men on antiretroviral therapy compared with an HIV-uninfected control group. The incidence of prediabetes and diabetes was increased by nearly 2 fold and 3 fold, respectively, among antiretroviral-therapy-treated men, compared with HIV-uninfected men, following adjustment for age and body mass index. Finally, among the antiretroviral-therapy-treated men, use of a PI, efavirenz, or stavudine was each significantly associated with an increased risk for prediabetes or diabetes. Howard and colleagues took the investigation of diabetes a step further by performing oral glucose tolerance testing in a group of HIV-infected and at-risk HIV-uninfected women with no histories of diabetes (Abstract 701). The prevalence of diabetes overall in this cohort of predominantly minority women (38% who had a family history of diabetes) was 6%, whereas 11% had impaired glucose tolerance. HIV infection, PI use, and antiretroviral use did not appear to increase the risk of diabetes or of abnormal glucose tolerance. In a multivariate model, only age greater than 50 years and smoking were predictive of an abnormal glucose tolerance test after controlling for HIV serostatus, antiretroviral therapy or PI use, race, and family history of diabetes. This study, which used more sensitive measures of glucose homeostasis, suggests that traditional risk factors may play a greater role than HIV infection or use of specific antiretroviral drugs in the development of impaired glucose tolerance.

Diabetes may also contribute to the neurologic sequelae of HIV infection. A cohort study (Abstract 502) examined factors associated with overall cognitive function in an aging cohort of HIV-infected adults and found that diabetes was more common among older HIV-infected people and was associated with worse overall cognitive function and psycho-motor functioning after controlling for age, antiretroviral therapy, existing hypertension, elevated cholesterol level, and smoking.

Lipoatrophy and Lipohypertrophy

Limited data exist on the risk of lipoatrophy from controlled trials in antiretroviral-naive patients. Podzamczer and colleagues reported 48-week data from a prospective randomized trial that included objective measures of body fat assessed by DEXA scans (Abstract 715). In this study, 237 patients were randomized to receive efavirenz/lamivudine combined with either stavudine or abacavir. Although virologic and immunologic responses were similar, a greater proportion of the stavudine-treated patients (20%) than abacavir-treated patients (2.7%) noted subjective evidence of lipoatrophy in at least 1 body area at 48 weeks. These observations were confirmed among the 78 subjects who underwent DEXA scanning at baseline and 48 weeks. Among stavudine-treated, compared with abacavir-treated, patients, fat loss by DEXA was greater overall (-1152 g vs. + 1749 g, respectively) and in both the arms (-177 g vs + 136 g) and in the legs (-1234 g vs + 519 g), respectively. These data confirm those from earlier trials suggesting an increased risk of developing lipoatrophy with stavudine-containing treatment. Longer follow-up is needed to determine the risk of lipoatrophy among the abacavir-treated patients. The identification of antiretroviral therapy regimens with low-risk of lipoatrophy over long follow-up is eagerly awaited.

The only treatment option that has been previously shown to be promising for patients with lipoatrophy has been the substitution of stavudine with abacavir or zidovudine (Carr, *JAMA*, 2002; McComsey, *Clin Infec Dis*, 2004). Preliminary results from studies of rosiglitazone, an insulin-sensitizing

drug, have shown conflicting results (Sutinen, *Lancet*, 2003; Hadigan, 2nd IAS, 2003).

Carr reported the results of a randomized, placebo-controlled trial evaluating a 4 mg twice-daily dose of rosiglitazone in subjects with clinical lipoatrophy on antiretroviral therapy. Following 48 weeks of treatment, although there was evidence of improvement in insulin sensitivity in the rosiglitazone-treated subjects, there was no evidence of any effect of rosiglitazone on limb fat. In addition, rosiglitazone treatment was associated with high rates of hypertriglyceridemia. Why did these investigators see no benefit when the earlier study by Hadigan and colleagues, reported last summer in Paris, suggested an improvement in insulin sensitivity and limb fat with rosiglitazone treatment? Possible explanations include the requirement of documented insulin resistance as an entry criterion in the Hadigan study. Nonetheless, this recent study suggests that rosiglitazone therapy offers little improvement in limb fat among an unselected group of subjects with lipoatrophy.

Recombinant human growth hormone (rhuGH) at a dose of 4 mg/day for 12 weeks was previously shown to reduce trunk fat, visceral adipose tissue, total cholesterol, and non-HDL-c in subjects with fat accumulation on antiretroviral therapy; however, the improvement reverted after the drug was stopped. Kotler reported the results of a large, randomized study comparing 1 mg/day or 2 mg/day of rhuGH as maintenance therapy for up to 60 weeks among patients who had previously received higher doses of rhuGH (Abstract 80). Following 60 weeks of treatment, significant reductions in trunk fat, total cholesterol, and non-HDL-c were maintained. There was no change in limb fat or insulin resistance noted. The only difference between the two dose groups was a higher rate of arthalgia in the 2-mg dose group. Further investigation of low-dose rhuGH is currently under way.

Bone Density

The relationships among HIV infection, antiretroviral therapy, and osteoporosis remain unclear. Data from the Womens Interagency HIV Study (WIHS) demonstrated that the prevalence of osteopenia/osteoporosis was 3-fold higher among HIV-infected women than among HIV-uninfected women. Among the women with HIV infection, older age, white race, postmenopausal status, and lower body mass index were associated with lower bone density; longer duration of nevirapine exposure appeared to be associated with higher bone density in this cohort. Whether the reduced bone mineral density reported in some studies of HIV-infected patients will translate into higher rates of pathologic fractures over time remains to be seen. McComsey reported on a series of 49 patients with fractures collected from 9 large HIV clinics serving an estimated 8600 patients, and found that most of these patients had not received an adequate work-up for osteopenia, indicating the need for better education of HIV providers on the management of these types of fractures (Abstract 743).

Cardiovascular Complications

The long-term consequences of the metabolic complications of antiretroviral therapy on cardiovascular risk remain a topic of great interest. At this year's conference, follow-up data from previously reported studies confirmed previous observations. Investigators from the Data collection on Adverse events of Anti-HIV Drugs study group reported an increase in the relative risk of cardiovascular and cerebrovascular events with longer exposure to combination antiretroviral therapy (Abstract 737). In addition, this group reported that the Framingham risk equation came close to predicting the observed rate of events. The HIV InSight database found a link between cumulative exposure to PI therapy and cardiovascular disease (Abstract 736), but the ongoing Kaiser study continued to show a relationship between HIV infection and risk of hospitalization for coronary heart disease, and for the first time, a link between duration of PI therapy and coronary heart disease (Abstract 739).

Studies of subclinical atherosclerosis that employed measurements of carotid intimal medial thickness and coronary calcification by computed tomography scan also found that traditional risk factors, rather than PI exposure per se, appeared to be associated with these surrogate markers for atherosclerotic disease (Abstracts 738,734). However, 1 cross-sectional study found a strong relationship between exposure to PIs and the development of carotid plaques (Abstract 735). Longer-term follow-up of these cohorts is eagerly awaited.

Previous small studies have suggested that PI-based therapy might increase the risk of hypertension. However, a longitudinal analysis of the DAD study found that although there was a high prevalence of hypertension in HIV-infected patients, traditional risk factors (male sex, higher body mass index, and older age) but not duration of use of any class of antiretrovirals predicted the development of hypertension over an average follow-up time of 1.5 years (Abstract 75). In a smaller study on hypertension from WIHS, the prevalence of hypertension appeared similar between the HIV-infected and HIV-uninfected groups; however, antiretroviral therapy did appear to be associated with an increase in the incidence of hypertension among women over a longer period of observation (Abstract 741).

Hepatitis Virus Coinfection

Hepatitis C Virus Treatment Trials: RIBAVIC, APRICOT, and ACTG 5071

Three large randomized trials examining the activity of interferon alfa and ribavirin combinations for HIV and hepatitis C virus (HCV) coinfection provided the largest and most informative experience to date of treatment outcomes (Abstracts 117LB, 112, 110). The primary focus of these trials was the proportion of patients achieving sustained virologic response (SVR) defined as undetectable HCV RNA 24 weeks following cessation of therapy. Although the results varied slightly between these trials due to differing patient populations and specific regimens, there was consensus on the following points: The combination of pegylated interferon alfa (PEG-IFN) and

ribavirin was the most efficacious combination; patients with genotype 1 had inferior responses to those with other genotypes; virologic response at week 12 predicted sustained virologic response; and sustained virologic responses were lower than those reported for HIV-uninfected patients. Other important observations included the lack of antagonism between ribavirin and zidovudine, stavudine, or lamivudine, and the histological response rate (33%) observed in patients without an SVR in ACTG 5071. These trials are summarized in Table 1.

In the ANRS RIBAVIC study (Abstract 117LB), 412 patients (79% injection drug users) with CD4+ cell counts greater than 200/µL were randomized PEG-IFN to a 48-week treatment course of PEG-IFN (the 2b form) plus ribavirin (800 mg/day, approximately 12/mg/kg/day) or interferon alfa (IFN; 2b) plus ribavirin. Among study participants, 58% had genotypes 1 or 4, 34% had genotype 3 and 8% had other genotypes. An SVR occurred in 26% of the PEG-IFN–treated patients and in 18% of the IFN-treated patients ($P = 0.031$). Res- ponse rates were lower in genotypes 1 or 4 (15%) compared with others (43%). Virologic response at week 12 predicted SVR. Treatment discontinuation occurred in 42% of patients but did not differ between the groups.

The APRICOT study enrolled patients from nearly 20 countries and 100 centers to a 48-week course of IFN (2a form) plus ribavirin (n = 285) or PEG-IFN (the 2a form) (n = 286) or PEG-IFN plus ribavirin (n = 289) (Abstract 112). The ribavirin was administered in a blinded fashion. Sixteen percent of patients had cirrhosis, and 61% had genotype 1. An SVR was achieved in 40% of subjects receiving PEG-IFN plus ribavirin, 20% receiving PEG-IFN alone, and in 12% receiving IFN plus ribavirin. All comparisons between groups were highly significant. For patients infected with genotype 1, SVR occurred in 29% of the PEG-IFN plus ribavirin group and in 62% of the patients with genotypes 2 or 3 in this group. Twenty-five percent of patients withdrew early from treatment in the PEG-IFN plus ribavirin arm, mostly due to adverse events or non-safety related reasons. The most common adverse events attributed to the study drug were fatigue, fever, headache, and myalgia. Depression was reported in 20%. CD4+ cell count levels dropped a median of 140/µL, but CD4+ percentage did not change, and there were no reports of opportunistic infections. Although not required by the protocol, 85% of patients on this study were receiving antiretroviral therapy. In a nested pharmacokinetic study evaluating for potential interac-

Table **1.** Baseline Characteristics and Sustained Virologic Response in Pegylated Interferon Alfa plus Ribavirin Treatment Arms from the RIBAVIC, APRICOT, and ACTG 5071 Studies

	RIBAVIC (Abstract 117lb)*	**APRICOT** (Abstract 112) †	**ACTG 5071** (Abstract 110) ‡
Baseline Characteristics	(N=207)	(N=289)	(N=66)
Male	77%	80%	79%
White	n/a	80%	50%
Age (years)	39	40	45
CD4+ cells/µL	527	520	492
Antiretroviral therapy	82%	85%	85%
Hepatitis C virus RNA	5.9 x 10^6 IU/mL	5.6 x 10^6 IU/mL	6.2 x 10^6 IU/mL
Hepatitis C virus genotype 1	58% §	61%	77%
Cirrhosis	40%	15%	11%
Sustained Virologic Response			
All patients	27%	40%	27%
Genotype 1 only	15%§	29%	14%

* Pegylated interferon alfa 2b 1.5 µg/kg weekly plus ribavirin 800 mg/day.
† Pegylated interferon alfa 2a 180 µg/weekly plus ribavirin 800 mg/day.
‡ Pegylated interferon alfa 2a 180 µg/weekly plus ribavirin in dose escalation from 600 mg/day to 1000 mg/day.
§ Includes genotype 1 and genotype 4.
n/a indicates not available.

tions between ribavirin and either zidovudine, stavudine, or lamivudine (Abstract 136LB), measurements of serum and intracellular levels of these drugs revealed no evidence for antagonism.

ACTG 5071 randomized 134 patients at 21 centers to either PEG-IFN (2a) plus ribavirin or IFN (2a) plus ribavirin (Abstract 110). Of note, ribavirin was administered in a dose escalation schedule starting with 600 mg/day and increasing as tolerated to 1000 mg/day. In this study, 77% of subjects had genotype 1, and 11% had cirrhosis. Twenty-seven percent of patients randomized to PEG-IFN plus ribavirin and 12% of patients receiving IFN plus ribavirin ($P < 0.001$) had an SVR. Response rates for genotype 1 were 14% and 6%, respectively for the 2 groups. Among the patients with early virologic response (ie, a 2-log reduction of HCV RNA at 12 weeks), 51% had an SVR. None of the patients without early virologic response had an SVR.

One of the most interesting analyses from this study evaluated the histologic response in those individuals without an SVR. All samples were blinded and reviewed by the same pathologist. Approximately one-third of patients without an SVR showed evidence of histologic improvement with treatment. Although the clinical significance of this finding remains unknown, it raises many questions regarding pathogenesis and avenues for alternate treatment strategies. Of interest was a study by Rodriguez that showed histologic improvement in patients in whom treatment had initially failed by virologic response criteria who then received an additional 24-week course of treatment with PEG-IFN interferon and ribavirin (Abstract 821).

Host Factors Associated with Natural History of HCV and Response to Treatment

Several abstracts evaluated immune correlates of outcome in patients with HCV coinfection. In the ACTG 5071 study, sequential single cell cytokine assays performed on a subset of study participants showed an overall reduction in HCV-specific responses during treatment, and a correlation between preservation of Th1 responses at week 24 and SVRs (Abstract 111). In a small study of intrahepatic lymphocyte responses from the liver biopsies obtained from patients in ACTG 5071, both CD4+ cell count and CD8+ cell count responses to HCV were detected at frequencies similar to those seen in HCV-monoinfected patients (Abstract 113). Host genetic factors were evaluated in an ACTG 5071 substudy of DNA polymorphisms thought to be involved in host inflammatory reactions and fibrosis. Predictors of liver fibrosis were found with genotype for the CCR5 promoter, tumor growth factor (TGF) beta, and interleukin-13 ([IL-13]; Abstract 116). In acute HCV infection, loss of HCV specific interferon gamma production was associated with persistent viremia in 1 study (Abstract 788). Low CD4+ nadir was associated with loss of HCV-specific responses and persistence of HCV during acute infection in another study (Abstract 790).

Hepatitis Virus and HIV Disease Progression

The relationship between hepatitis virus infection (treated or untreated) and HIV disease progression and response to antiretroviral therapy was examined in the EuroSIDA cohort (Abstract 799). In 5883 patients, HCV was present in 34% and hepatitis B virus (HBV) in 9%. Liver–related mortality increased in patients with hepatitis but not overall deaths. There was no detectable difference in response to antiretroviral therapy in patients with or without hepatitis. These results are in contrast to those from an evaluation of patients from Argentina participating in antiretroviral naive studies, in which hepatitis virus infection was associated with a blunted CD4+ cell response (Abstract 817). In a US-based study of more than 12,000 veterans with an HCV seroprevalence of 38%, HCV (independent of injection-drug use) was associated with increased risk for mortality (Abstract 800). Although these studies of different cohorts showed slightly differing conclusions, they all point to the increasingly important role that hepatitis virus coinfection plays in the natural history and treatment strategies for HCV and HIV coinfection.

Hepatitic Steatosis in HCV Infection

Several studies looked at the predictors of hepatitic steatosis and their relationship to hepatitic fibrosis. Previous reports suggested that steatosis is associated with increased fibrosis progression and diminished response to therapy. In an evaluation of 113 patients presented to the Johns Hopkins University clinic who met criteria for biopsy, grade 2 steatosis was identified in only 5% of subjects. Steatosis was associated with stavudine use, cumulative PI exposure, weight greater than 190 lbs, CD4+ cell count below 200/µL, HIV suppression, and white race. In contrast, 56% of 48 patients seen at Cornell University showed evidence of steatosis that was associated with more advanced fibrosis (Abstract 812). Factors identified in the Johns Hopkins University study were not identified as predictors of steatosis in the Cornell University study. Sampling and patient characteristics may explain some of these differences, but clearly more data are needed to understand the predictors and significance of steatosis in HIV and HCV coinfection.

Hepatitis B Virus

Several abstracts on treatment of HBV extended prior observations on the activity of adefovir, tenofovir, and emtricitabine. The TECOVIR study evaluated serum markers of HBV in a cohort of patients receiving tenofovir as part of their antiretroviral regimen (Abstract 834). HBV DNA was detectable in 88% of the 119 patients at baseline. After a median of 9 months, HBV was undetectable in 32% of patients. In the 3-year follow-up of the adefovir (10 mg/day) study for the treatment of HBV, 46% of patients had undetectable HBV DNA (Abstract 835). Increased duration of treatment was associated with an increased response, and not with rebound or viral resistance to adefovir. In a study of patients with HBV who enrolled in an emtricitabine-containing antiretroviral treatment trial, 82% of the 24 patients had a 5-log reduction in HBV DNA (Abstract 836).

Other Coinfections: HSV, Malaria, and Tuberculosis

A session dedicated to global AIDS led off with 2 excellent mini-lectures covering herpes simplex virus (HSV) and the global epidemiology of HIV (Abstract 142) and the interaction between HIV and malaria (Abstract 143). Despite the prevalence of these infections worldwide and their copresence in HIV-infected persons, they have received relatively little attention. In her overview of HSV and HIV, Celum pointed out that numerous epidemiologic studies have found a link between the prevalence of HSV-2 and the risk of HIV acquisition. Across these studies, including the Rakai, Uganda, study of HIV-serodiscordant couples, the presence of HSV-2 in the HIV-uninfected partner was associated with a 2-fold to 4-fold increased risk of HIV seroconversion. Acyclovir prophylaxis is known to reduce HSV recurrence rates. With HSV prevalence rates in many parts of Africa in excess of 60% to70%, prophylaxis of HSV is 1 possible approach to reducing HIV transmission that will be tested in upcoming clinical trials.

Malaria may also play a role in increasing HIV transmission by causing profound anemia (which increases the requirement for blood transfusions where the blood supply is not adequately screened) and by prenatal transmission. Pregnant women and HIV-infected persons with low CD4+ cell counts appear to have more severe malaria. Response to antimalarial treatment in persons with HIV infection is an understudied area, and resistance to current widely prescribed malarial treatment regimens remains a huge challenge for malaria control. As trimethoprim-sulfamethoxazole prophylaxis and antiretroviral therapy programs are initiated in Africa, much needs to be learned about the optimal treatment of coinfection.

HIV and tuberculosis (TB) coinfection was the topic of an epidemiologic study from Rio de Janeiro, Brazil (Abstract 147). The incidence and outcome of HIV and TB were examined from 1995 and 2002 through review of surveillance databases. Temporal trends of AIDS and death paralleled the introduction of antiretroviral therapy. Although there was a slight decrease in the proportion of AIDS patients who developed TB after 1995, between 1999 and 2001 the overall proportion of AIDS patients with TB as a secondary cause of death remained stable at around 18%. TB thus remains a major contributor to mortality in the antiretroviral era in Rio de Janeiro.

The high rates of mortality associated with TB in regions without access to antiretroviral therapy were highlighted in a presentation from Chennai, India (Abstract 764). Among the 95 patients followed up, 42% had died by 24 months. Among the survivors, a second episode of TB occurred in 39%. Results from molecular fingerprinting studies revealed that these cases were all due to reinfection with a second strain of TB.

Interactions between the rifamycins and NNRTIs and PIs complicate the management of patients requiring simultaneous treatment for both HIV and TB. When efavirenz is administered with rifabutin, a dose increase of rifabutin from 300 mg twice weekly to 600 mg twice weekly is recommended to compensate for the effects of efavirenz on rifabutin levels. The effect of this dose adjustment was evaluated in a pharmacokinetic study of 15 HIV-infected patients initiating an efavirenz-based antiretroviral regimen following the start of a rifabutin-containing TB regimen (Abstract 761). With the dose increase of rifabutin to 600 mg, mean area-under-the-concentration-curve (AUC) levels of rifabutin in the presence of efavirenz were similar to levels of rifabutin in the absence of efavirenz. Cmax levels of rifabutin were higher at the 600 mg dose but were not associated with increased toxicity.

Management of HIV and TB disease is also complicated by immune reconstitution syndromes (IRIS). In a retrospective study of 37 patients with HIV and TB in Paris, France, 43% had evidence of IRIS between 1996 and 2001 (Abstract 757). The strongest predictors of IRIS were the presence of disseminated TB (≥2 organs involved), low CD4+ cell count (<200/μL) and high HIV RNA (>100,000 copies/mL). The timing of initiation of antiretroviral therapy in relation to the start of TB therapy was similar between the groups of patients who did and did not experience IRIS. In another study of TB treatment regimens, IRIS was reported in 22% (Abstract 763).

Complications of Antiretroviral Therapy During Pregnancy

The safety of antiretrovirals for both mother and infant continues to be monitored as more experience is accumulated for the highly effective combination regimens currently being utilized during pregnancy. The preponderance of data presented at the conference suggested that antiretroviral regimens were not associated with increased mortality or toxicity for infants. For pregnant women, concern still exists about the rare but serious hepatitic toxicity associated with nevirapine, particularly for women with high CD4+ cell counts.

The Pediatric ACTG (PACTG)1022 study randomized 38 pregnant women to a nelfinavir- or a nevirapine-containing regimen (Abstract 938). Zidovudine/lamivudine was the nRTI backbone for the regimen. Treatment-limiting toxicity occurred in 1 of 21 nelfinavir recipients and 4 of 17 nevirapine recipients. Hepatotoxicity was the treatment-limiting toxicity in the women receiving nelfinavir and in 3 of 4 of the women receiving nevirapine. One woman receiving nevirapine died of fulminant hepatitic failure. This woman had normal liver enzyme levels at the start of therapy and did not have HBV or HCV infections. The fourth woman who had nevirapine toxicity developed a Stevens-Johnson syndrome. All of the women with nevirapine treatment-limiting toxicity had CD4+ cell counts of greater than 250/μL at the time of therapy initiation. Although this study had small numbers and differences were not statistically significant, the trial will be modified in view of the recent warning letter about potential for increased nevirapine toxicity in women with CD4+ cell counts above 250/μL.

Another small study from the United States failed to detect increased risk of toxicity from nevirapine administered during pregnancy (Abstract

939). This was a retrospective study of 41 pregnant and 221 nonpregnant women who received nevirapine. The median CD4+ cell count was 474/µL for the pregnant women and 289/µL for the nonpregnant women. Serious adverse events occurred more frequently in the nonpregnant women (6.5%) than in the pregnant women (0%). There were no deaths reported.

Two studies examined the relationship among nRTI use, pregnancy, lactic acid elevations, and adverse outcomes among infants. The first study compared 100 children born to HIV-infected mothers with 24 children born to HIV-uninfected mothers (Abstract 941). Elevated lactate levels (2.5 mmol/L or higher) were present in approximately two-thirds of children born to HIV-infected mothers, compared with none of the children born to HIV-uninfected mothers. All elevated lactate levels returned to normal after 3 months, and no children developed neurologic symptoms during the follow-up period. In a second study from Italy, 53 infants born to HIV-infected mothers were compared with 20 infants born to HIV-uninfected mothers (Abstract 942). In contrast to the prior study, elevated lactate levels were detected among 20 infants born to HIV-uninfected mothers (40%) at a frequency similar to infants born to 53 HIV-infected mothers. Among the 53 infants born to HIV-infected mothers, 21 were exposed in utero to 2 nRTIs, and 32 to potent antiretroviral therapy. A higher proportion of infants born to HIV-infected mothers had lactate levels above 5 mmol/L compared with controls, but all elevated lactate levels in both groups resolved by 6 months. There were also no differences in mitochondrial PBMC DNA content between the groups. Similar to the first study, there were no clinical abnormalities detected.

Finally, two large studies examined the frequency of prematurity/low birth weight outcomes among women receiving antiretroviral therapy during pregnancy. The first study analyzed data from more than 23,500 pregnancies from the US-based Antiretroviral Pregnancy Registry, which formed in 1989. There was no difference in the frequency of low birth weight infants (<2500 g) or prematurity (<37 weeks' gestation) born to women receiving a PI-containing regimen versus a non-PI-containing regimen. There was a small increase (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.02-5.39) in very low birth weight (<1500 g) infants, but the overall incidence of this complication was low (3% vs. 1%). In a European Collaborative Study, pregnancy outcomes in 1415 women were evaluated in 9 countries from 1998 to 2002. The proportion of premature births increased: from 14% between 1994 and 1997 to between 27% and 31% between 1998 and 2002. Very low birth weight infants increased from 0.5% to 6% during these same intervals. Although the conclusion of this study differed from the US study, there was discussion during the session regarding potential confounding factors that may have influenced the findings from the later study.

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Top HIV Med, 2004; Volume 12(1):31-39

Conference Abstract numbers, titles, and authors appear at the end of the issue.

Additional Suggested Reading

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Conference Abstracts Cited in This Issue

The full text of all abstracts is available online at www.retroconference.org.

2. Multinational Business Responding to AIDS in South Africa. Gavin Churchyard, S Charalambous, A D Grant, L Pemba, D Martin, R Wood, J Sim, R Chaisson, and B A Brink.

6. Cellular Factors and HIV Budding. Wesley I Sundquist.

15. Functional and Phenotypic Heterogeneity of Memory CD4 T Cells Are Dictated by Antigen Persistence and Load. A Harari, F Vallelian, S C Zimmerli, and G Pantaleo.

20. The "Screening and Tracing Active Transmission" Program: Real-time Detection and Monitoring of HIV Incidence. C Pilcher, E Foust, J McPherson, R Ashby, J Owen-O'Dowd, T Nguyen, R Lee, S Fiscus, and P Leone.

21. Incidence of HIV Superinfection Following Primary Infection. D Smith, J Wong, G Hightower, K Kolesch, C Ignacio, E Daar, D Richman, and S Little.

23. Effect of Treatment during versus after Acute Retroviral Syndrome (ARS) on HIV Viral Load and CD4 Cell Counts within 3 Years of Infection. N Voirin, D Smith, J P Routy, M Legault, D Baratin, C Trepo, L Cotte, J M Livrozet, J L Touraine, D A Cooper, A Gayet-Ageron, J Ritter, J Fabry, and P Vanhems.

24. Limited Durability of Immune Control following Treated Acute HIV Infection. D Kaufmann, M Lichterfeld, M Altfeld, T Allen, M Johnston, P Lee, B Wagner, E Kalife, D Strick, E Rosenberg and B D Walker.

35LB. Continuing High-risk Sexual Behavior and Increasing Antiretroviral Resistance among HIV+ Patients in Care Helps Explain the Rising Prevalence of Resistance among New HIV Infections. M Kozal, R Amico, J Chiarella, T Schreibman, D Cornman, W Fisher, J Fisher, and G Friedland.

36LB. Persistence of Transmitted Drug-resistant Virus among Subjects with Primary HIV Infection Deferring Antiretroviral Therapy. S J Little, K K Koelsch, C C Ignacio, J K Wong, Y Lie, S D W Frost, and D D Richman.

37. Emergence and Long-term Persistence of NNRTI-resistant Variants in Patients Starting and Stopping NNRTI-containing Regimens. S Palmer, V Boltz, F Maldarelli, E Halvas, J Mican, J Mellors, and J Coffin.

39. Low-frequency NNRTI-resistant Variants Contribute to Failure of Efavirenz-containing Regimens. J Mellors, S Palmer, D Nissley, M Kearney, E Halvas, C Bixby, L Demeter, S Eshleman, K Bennett, S Hart, F Vaida, M Wantman, J Coffin, and S Hammer for the ACTG 398 Study Group.

40LB. A Randomized, Double-blind Trial Assessing the Efficacy of Single-dose Perinatal Nevirapine Added to a Standard Zidovudine Regimen for the Prevention of Mother-to-child Transmission of HIV-1 In Thailand. M Lallemant, G Jourdain, S Le Coeur, J Y Mary, N Ngo-Giang-Huong, S Koetsawang, S Kanshana, K McIntosh, V Thaineua, and the Perinatal HIV Prevention Trial (Thailand).

41LB. Exposure to Intrapartum Single-dose Nevirapine and Subsequent Maternal 6-Month Response to NNRTI-based Regimens. G Jourdain, N Ngo-Giang-Huong, P Tungyai, A Kummee, C Bowonwatanuwong, P Kantipong, P Lechanachai, S Hammer, M Lallemant, and Perinatal HIV Prevention Trial Group.

44. Enhancement of HIV Infection by Activated Dendritic Cells Occurs via Trafficking through a CD81 Enriched Compartment. David McDonald, T J Hope.

45. HIV-1 Spread between T Cells via a Virological Synapse. Quentin J Sattentau and C Jolly.

46. HIV Assembly in, and Release from, Primary Macrophages. Mark Marsh, A Pelchen-Matthews, B Kramer, R Byland, M Deneka, and A Fraile-Ramos.

51. Poor Virologic Responses and Early Emergence of Resistance in Treatment Naive, HIV-infected Patients Receiving a Once Daily Triple Nucleoside Regimen of Didanosine, Lamivudine, and Tenofovir DF. J Jemsek, P Hutcherson, and E Harper.

52. Low Genetic Barrier to Resistance Is a Possible Cause of Early Virologic Failures in Once-Daily Regimen of Abacavir, Lamivudine, and Tenofovir: The Tonus Study. R Landman, G Peytavin, D Descamps, F Brun Vezinet, H Benech, A Benalisherif, A Trylesinski, C Katlama, P M Girard, F Raffi, P Yeni, M Bentata, B Jarrousse, C Michelet, P Flandre, and the Tonus Study Group.

53. COL40263: Resistance and Efficacy of Once-daily Trizivir and Tenofovir DF in Antiretroviral Naïve Subjects. R Elion, C Cohen, E DeJesus, R Redfield, J Gathe, R Hsu, L Yau, L Ross, B Ha, R Lanier, T Scott, and COL40263 study team.

54. K65R: A Multinucleoside Resistance Mutation of Increasing Prevalence Exhibits Bi-directional Phenotypic Antagonism with TAM. U Parikh, D Koontz, N Sluis-Cremer, J Hammond, L Bacheler, R Schinazi, and J Mellors.

55. The HIV-1 K65R RT Mutant Utilizes a Combination of Decreased Incorporation and Decreased Excision to Evade NRTI. K L White, N A Margot, J M Chen, R Wang, M Pavelko, T Wrin, C J Petropoulos, M McDermott, S Swaminathan, and M D Miller.

56. Randomized, Placebo-Controlled Trial of Abacavir Intensification in HIV-1-infected Adults with Plasma HIV RNA <500 Copies/mL. S Hammer, R Bassett, M Fischl, K Squires, L Demeter, J Currier, G Morse, V DeGruttola, C Lalama, S Snyder, J Mellors, ACTG 372A Study Team, and Adult AIDS Clinical Trials Group.

57. Detection of Pre-existing Minority Viral Populations Contributing to the Evolution of Resistance to Protease Inhibitors. C Charpentier, L Morand-Joubert, G Chêne, P-M Girard, F Clavel, and A J Hance.

58. A 16-week Treatment Interruption Does Not Improve the Virologic Response to Multidrug Salvage Therapy in Treatment-experienced Patients: 48-week Results from ACTG A5086. C Benson, G Downey, D V Havlir, F Vaida, M Lederman, R Gulick, M Glesby, S Patel, M Wantman, C Bixby, C Pettinelli, A Rinehart, S Snyder, J Mellors, and the ACTG A5086 Study Team.

62. HIV-1 Vif Overcomes the Innate Antiviral Activity of APOBEC3G by Promoting its Degradation in the Ubiquitin-Proteasome Pathway. A Mehle, B Strack, P Ancuta, and D Gabuzda.

63. Characterization of Mutations Generated by APOBEC3G on HIV-1 DNA. Q Yu, R König, S Pillai, M Kearney, S Palmer, D Richman, J Coffin, and N R Landau.

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HIV-1 gp41 Associated with Long-term Enfuvirtide Therapy. L Xu, A Pozniak, A Wildfire, D Ratcliffe, J Workman, A Joall, E Smit, P A Cane, and D Pillay.

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