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IN THIS ISSUE

Highlights from the 6th Conference on Retroviruses and Opportunistic Infections, January 31 – February 4, 1999

ABOUT THIS ISSUE...

This issue of *Improving the Management of HIV Disease* is the first of several issues to be published in 1999. The issue contains a timely review of the new information that was presented at the 6th Conference on Retroviruses and Opportunistic Infections, held in Chicago from January 31-February 4, 1999. Again this year, the Conference provided an important forum for basic science and clinical science investigators to present, discuss, and critique developments in the field of human retrovirology and opportunistic complications.

This special issue provides a review of much of the important research that was presented at the conference. Dr Mario Stevenson summarizes the basic science studies discussed at the conference. Dr Bruce Walker reviews new data regarding HIV pathogenesis. Drs Judith Currier and Diane Havlir provide an update of the epidemiology, changing characteristics and presentation, and prevention and treatment of the spectrum of HIV-related complications. Finally, Drs Eion Coakley, Roger Inouye, and Scott Hammer give a thorough review of the new data in the area of antiretroviral drug management in HIV disease. A listing of the Conference abstracts for the presentations that are discussed by the authors of these reviews can be found at the end of the publication.

Upcoming issues of this publication will summarize the presentations of the International AIDS-Society-USA seventh annual series, *Advanced CME Course in HIV Pathogenesis, Antiretrovirals, and Selected Issues in HIV Management.* Please call the International AIDS Society-USA conference information line, 415-561-6725.

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Presidio of San Francisco
1001 B O'Reilly Avenue, Box 29916
San Francisco, CA 94129-0916
Phone: (415) 561-6720
Fax : (415) 561-6740
email: info@iasusa.org

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CONTRIBUTORS

Eion P. G. Coakley, MD
Harvard Medical School and Beth Israel-Deaconess Medical Center

Judith S. Currier, MD
University of Southern California and UCLA Care Center

Scott M. Hammer, MD
Columbia University College of Physicians and Surgeons

Diane V. Havlir, MD
University of California San Diego

Roger T. Inouye, MD
Harvard Medical School and Beth Israel-Deaconess Medical Center

Mario Stevenson, PhD
University of Massachusetts Medical Center

Bruce D. Walker, MD
Harvard Medical School and Massachusetts General Hospital

STAFF AND CONTRIBUTORS

Executive Director . . . . . **Donna M. Jacobsen**
Operations Manager . . . . . **Misako E. Hill**
Manuscript preparation . . . . . **Christopher Adams**
Copy/Proofreading . . . . . **Mu'frida Bell; David Sweet**
Printing . . . . . **Golden Street Printing**

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HIGHLIGHTS OF BASIC SCIENCE RESEARCH

Mario Stevenson, PhD

Basic science contributions continue to represent an important and expanding feature of the Conference. New insight into the mechanism of action of the major regulatory protein, Tat, has been disclosed in the past year, and several presentations focused on the interaction of Tat with cellular proteins and how they impact on Tat function and the species-specific nature of Tat action. A number of presentations on the viral accessory gene products, particularly Vpr and Nef, revealed how these proteins influence the physiology of the target cell, and how these activities can influence the extent of virus replication and the ability of virus-infected cells to evade the immune response. Studies on chemokine receptors and how the level of chemokine-receptor expression influences viral transmission, tropism, and disease progression were featured in several sessions at the Conference. Biochemical and crystallographic analysis of viral structural proteins are leading to a better understanding of how these proteins mediate their action and ultimately may point to new approaches to inhibiting the action of the viral proteins.

ACCESSORY GENES

The accessory proteins of primate lentiviruses represent one of the most intensely studied areas of primate lentivirus biology, yet identification of the actual roles played by these proteins in primate lentiviral replication remains elusive. Inactivation of the accessory genes has been shown to impair viral replication and pathogenicity in infected monkeys to varying degrees. Thus, inactivation of *vif* has the greatest impact on viral replication followed by *nef*, *vpx*, *vpr*, and *vpu* genes. Despite the fact that these accessory proteins are important for virus replication in the host, the role played by these proteins in virus replication is not well understood. In addition, these proteins represent attractive targets for the development of antiviral drugs. Since the accessory proteins are unique to the virus and there are as yet no known homologous functions encoded by the cell, drugs targeted at viral accessory proteins would be predicted to have little effect on host cell function.

Nevertheless, the accessory proteins have not yet been exploited as drug targets, primarily because there are no convenient in vitro assays that reconstitute their activity and can be employed in large-scale inhibitor screens. One important area of investigation regarding accessory protein function regards cellular intermediaries through which these accessory proteins mediate their action, and the identification of such factors may be the best approach to identifying how the accessory proteins participate in virus replication.

One presentation **(Abstract 60)** demonstrated that mice transgenic for Nef developed tumors as early as 4 months. The majority of mice with tumors had adenocarcinoma. These studies are similar to studies published in 1998 by Jolicoeur and colleagues **(*Cell* 95:163, 1998)** that Nef was pathogenic in a transgenic mouse setting. It is unclear how these transgenic models relate to the action of *nef* in virus-infected humans and monkeys, but they may provide useful information on pathways through which *nef* mediates this effect. Although it is clear that *nef* facilitates virus replication and pathogenicity in the host, how Nef promotes these activities is not well understood.

Two well-recognized features of *nef* activity in vitro are the abilities of *nef* to downregulate the expression of CD4 and MHC Class I from the cell surface. Downregulation of CD4 by Nef may impact the virus life cycle at several levels. Infected cells with less cell surface CD4 may be resistant to superinfection of the same cell by progeny virions. Intracellular sequestration of CD4 may influence cell activation pathways through modulating interaction of CD4 with its associated kinase p56 Lck and, further, may restrict the incorporation of CD4 into virions during virus maturation. Surface expression of MHC Class I is required for efficient cytotoxic T lymphocyte (CTL) recognition of the infected cell. Through MHC Class I downregulation, *nef* may influence susceptibility of infected cells to CTL recognition, perhaps affording the virus a longer residence in the host cell before it is destroyed by CTL.

Research presented at the Conference **(Abstract S22)** examined the mechanism through which *nef* induces MHC Class I downregulation. New studies demonstrate that *nef* stimulates endocytosis of MHC Class I molecules, resulting in their degradation in lysosomes. This modulation was induced by Nef proteins from primary and laboratory-adapted HIV-1 isolates by HIV-2 and SIV-Nef proteins. *nef* was found to interact with μ chains of adaptor complexes of the endocytic pathway. By interacting with the cell trafficking machinery, *nef* induces MHC downregulation that, in turn, may provide some measure of immune escape to the infected cell.

In addition to CD4 and MHC Class I downregulation, *nef* has been reported to augment viral infectivity in single-cycle infectivity assays. Kotov and colleagues **(Abstract S21)** presented studies that suggest that *nef* is present in HIV-1 cores at levels similar to those in virions. One prediction of this result is that *nef*, as a component of the viral core, may influence early events in the viral life cycle, such as formation of the reverse transcription complex or synthesis of viral cDNA. Kotov et al also demonstrated that *nef* regulates the pathway of virus entry. Thus, deletion of *nef* facilitates the infection of cells through an endocytic pathway. This would suggest that one action of *nef* is to ensure that virus infection proceeds through pH-independent fusion.

Studies identifying regions of *nef* that were required for downregulation of CD4 were presented **(Abstract 510)**. A highly conserved sequence in the C-terminal loop of *nef* exhibiting homology to dileucine-based protein sorting-signals was found to be important for the ability of *nef* to promote CD4 downregulation. In addition, mutation of the dileucine motif in *nef* also impaired the infectivity enhancement by *nef*. This dileucine motif was found to be necessary for interaction between *nef* and a subset of adaptor protein complex subunits. Thus, while previous studies suggest CD4 downregulation and infectivity enhancement may be genetically separable, these activities may both depend on an interaction between *nef* and adaptor protein subunits. HIV-Nef and SIV-Nef contain motifs that promote interaction with Src homology 2 and Src homology 3 domains of Src family protein tyrosine kinases. *nef* has also been shown to interact with cellular serine/threonine kinases. The ability of *nef* to interact with kinase cascades has led to the suggestion that *nef* may influence cellular signaling/activation pathways of the cell.

Studies presented at the Conference **(Abstract 509)** demonstrated that HIV-1 *nef* interacts with PAK kinase in infected macrophages and, to a lesser extent, T lymphocytes. Though previous studies suggested that *nef* interacts with the myeloid specific Src kinase, Hck, investigators did not observe *Nef-Hck* interaction in primary macrophages. The consequences of *Nef-PAK* interaction in macrophage lineage cells will await further studies to determine how PAK influences macrophage function.

Most of the studies with the accessory gene products dealt with Vpr. To date, at least 4 properties for Vpr have been published, including (1) a role for Vpr in promoting infection of nondividing macrophages; (2) induction of cell cycle G2 arrest; (3) association of Vpr with the DNA repair enzyme, uracil DNA glycosylase (UDG); and (4) induction of cell differentiation.

Chen and colleagues **(Abstract S20)** presented evidence for a novel activity of Vpr. Their studies demonstrated that when cells were transfected with a plasmid that had been damaged by exposure to ultraviolet irradiation, the presence of Vpr in the transfected cell promoted DNA repair of the ultraviolet-damaged template. As yet, it is unclear how the presence of Vpr promotes the ability of the cell to repair damaged DNA, or whether this activity is related to one of the known properties of Vpr such as association with uracil DNA glycosylase.

Studies suggesting a role for Vpr in promoting fidelity of HIV-1 replication were discussed **(Abstract 512)**. Using a viral shuttle vector containing the lacZα peptide gene as a reporter gene for mutations, a panel of Vpr variants was examined for their effect on mutation rate when Vpr is expressed in trans. Mutations that influenced association of Vpr with UDG impaired the ability of Vpr to influence the mutation rate. This effect was, however, found to be independent of virion incorporation. These studies suggest that Vpr acts through UDG to preserve the fidelity of reverse transcription. It is unclear whether this effect is related to the effect of Vpr on DNA repair synthesis as reported at the Conference by Chen and colleagues **(Abstract S20)**.

Pavlakis and colleagues **(Abstract S23)** presented evidence that Vpr promotes activation of the glucocorticoid receptor promoter. Residues in Vpr were identified that inactivate the ability of Vpr to activate the glucocorticoid promoter. Promoter activation by Vpr was found to be independent of the ability of Vpr to induce cell cycle arrest. A coactivator motif (LXXLL), which mediates glucocorticoid receptor-promoter activation, was identified.

Pavlakis and colleagues also presented evidence that Vpr-green fluorescent protein (GFP) fusion proteins rapidly underwent nuclear translocation, an observation that is consistent with the role of Vpr in nuclear targeting of viral DNA in nondividing cells. One group **(Abstract 581)** provided evidence that phosphorylation of HIV-1 Vpr is important for Vpr function. Virus-infected cells labeled with 32P-orthophosphate released virions containing phosphorylated Vpr. Phosphoamino acid analysis of serine mutants suggested that S79, S94, and S96 were phosphorylated.

Studies to determine which of the Vpr functions rely on Vpr phosphorylation are ongoing. One feature of Vpr-induced G2 arrest is that this property can be reconstituted in fission yeast, thus demonstrating a high evolutionary conservation of function. Vpr properties of cell cycle arrest, nuclear localization, and cell death/differentiation were examined

in fission yeast using a panel of Vpr mutations. Induction of cell cycle arrest was independent of nuclear localization and of cell killing. Only Vpr alleles that localized to the nucleus exhibited cell killing. Thus, fission yeast may be a useful model system to evaluate Vpr functions and pathways through which Vpr mediates its effect.

Emerman and colleagues **(Abstract 580)** presented evidence that the HIV-1 long terminal repeat (LTR) was more active in the G2 phase of the cell cycle. This is consistent with a model in which Vpr-mediated delay of G2 progression may promote higher levels of virus production for each round of the cell cycle. HIV-1 virions that expressed Vpr alleles competent for G2 arrest also replicated to higher levels (3- to 5-fold) in primary T cells compared with viruses that lacked Vpr or that contained mutants of Vpr that did not cause G2 arrest. Thus, Vpr may delay cells at a stage in the cell cycle when the LTR is most active and in which virus production is maximal.

Emerman and colleagues also presented studies **(Abstract 511)** aimed at identifying the mechanism through which Vpr produces cell cycle arrest. Cell cycle progression is dependent on activation of the mitotic cyclin-dependent kinase, cyclin B, which normally controls the entry of cells into mitosis. Activation of this kinase requires removal of inhibitory phosphates on threonine 14 and tyrosine 15 by the phosphatase, CDC 25C. Emerman et al demonstrated that Vpr interacts with this phosphatase, thus preventing it from activating cyclin B and mutations in Vpr, which impaired its cell-cycle arrest capacity and also its ability to interact with CDC 25C.

Several studies expanded on the exciting demonstration in the past year of cellular cofactors that mediate Tat transactivation. Cullen and colleagues **(Abstract L3)** presented a model that Tat simply serves as a recruitment factor for cellular proteins that promote transactivation of the LTR. In the past year, Jones and colleagues demonstrated that human cyclin T1 and its associated kinase, CDK9, comprise a coactivator complex (***Cell* 92:451, 1998**). Human cyclin T1 interacts with the activation domain of Tat, and Tat recruits the cyclin T complex to the LTR where cyclin T1 activates HIV-1 LTR-directed transcription.

Cullen and colleagues also presented evidence **(Abstract 507)** that cyclin T1, when recruited via a heterologous RNA protein interaction, was able to activate the LTR independently of Tat. Thus, Tat simply acts as a recruitment factor that directs cyclin T1 to the LTR, but activation of transcription is independent of Tat. The ability of cyclin T1 to be recruited to Tar by Tat was also shown to determine the species restriction of HIV Tat. Thus, mouse cells do not support efficient Tat transactivation, because mouse cyclin T1 could not efficiently be recruited to Tar. Substitution of a single amino acid within mouse cyclin T1 reversed the species restriction and permitted efficient Tat transactivation in mouse cells expressing the mutant cyclin T1. These findings were echoed by Gaynor and colleagues **(Abstract S24)**. These studies provide new insight into the workings of Tat and point to novel targets that may be exploited therapeutically.

VIROLOGY

The Bernard Fields Memorial Lecture was given by Sodroski, who summarized the recent crystallographic characterization of HIV-1 envelope glycoproteins. These studies have a considerable impact on AIDS research in general because of their potential to yield insight into how CD4 and coreceptor binding expose fusogenic domains in envelope that may provide new targets for antiretroviral agents. In addition, studies invoking a central role for envelope glycoprotein in HIV-1-mediated pathogenesis were discussed.

Hahn and colleagues **(Abstract S2)** presented exciting studies aimed at uncovering the origin of HIV-1. All HIV-1 strains known to infect humans were found to be closely related to one of the known SIV CPZ lineages that originate in the chimpanzee, *Pan troglodytes troglodytes*. Hahn presented a model to suggest the mechanism for the zoonosis. The use of monkeys as a food source by humans likely precipitated exposure to infected animal tissue for generations. However, infection of humans likely remained geographically isolated until the "bush meat" trade resulted in widespread distribution of animal tissue to population centers. This may explain why SIV CPZ, which has existed in monkeys for millennia, may have emerged as a zoonosis within the last 40 to 50 years. Since SIV CPZ infection of monkeys is nonpathogenic, the interaction of the virus with its natural host will be critical to the understanding of how HIV-1 is pathogenic in its human host.

Ho and colleagues **(Abstract 10)** used plasma apheresis to influence the equilibrium between virus production and virus clearance. The magnitude of the decrease in plasma viremia during apheresis reflects the added clearance rate mediated by the apheresis procedure relative to the clearance mediated by viral clearance mechanisms in the host. Using an established mathematical model of viral dynamics, HIV particle half-life for 4 HIV-1-infected subjects was found to be between 39 and 109 minutes. In parallel, the half-life of hepatitis C virus was found to be 100 to 182 minutes. Daily virion produc-

tion estimates that were previously based on a virion half-life of 6 hours will therefore have to be revised accordingly. It is as yet unclear why these half-life estimates differ from those featured in a recent publication by Martin and colleagues (***Nature Medicine* 5:211, 1999**). In those studies, viral clearance was measured following infusion of virion particles into SIV-infected and uninfected monkeys and was in the order of several minutes. The differences probably reflect the distinct approaches taken by these groups to investigate the dynamics of viral clearance, such as a more rapid clearance of particles prepared ex vivo and then reinfused.

Sundquist and colleagues **(Abstract L5)** presented detailed electron microscopic studies of HIV-1 virion cores that had been reconstituted in vitro. RNA and capsid-nucleocapsid fusion proteins spontaneously assemble into conical particles that resemble authentic viral cores both in terms of size and morphology. The lattices that are formed in these synthetic cores resemble those exhibited by icosahedral viruses. Studies of this kind are critical to the development of assays that can be employed to screen for inhibitors of virion core assembly.

Several presentations focused on the viral Gag matrix protein. This structural virion protein has generated intense interest among investigators because it appears to exhibit novel activities in the viral life cycle. Viral matrix proteins are well recognized for their role in virus assembly and in maintaining the integrity of the intact virion. However, primate lentiviral matrix proteins have been implicated in several stages of the virus life cycle. Thus, Gag matrix has been shown to promote incorporation of envelope glycoproteins into the maturing virion. Intriguingly, the matrix protein has been shown to play a critical role in viral infectivity. Mutations in matrix that do not influence either envelope incorporation or virion maturation have been shown to block viral infectivity and, in addition, Gag matrix has been shown to promote nuclear translocation of the viral reverse transcription complex following infection of the target cell. Consistent with these activities, matrix has been shown to tightly associate with the reverse transcription complex.

Aiken and colleagues **(Abstract S21)** and Sundquist and colleagues **(Abstract L5)** presented evidence that Gag matrix is contained within viral cores, findings that would be consistent with its reported role in governing the function of the reverse transcription complex. However, the suggestion that Gag matrix is incorporated into virion cores was challenged by Göttlinger and colleagues who failed to observe the presence of Gag matrix in highly purified cores from HIV-1 infected cells **(Abstract 508)**. The mechanism through which Gag matrix influences viral infectivity remains controversial. Freed and colleagues **(Abstract S38)** identified mutations in matrix that disrupt an early postentry step in the virus life cycle. The defect was manifest at the level of reverse transcription, again suggesting an important role for matrix in maintaining the integrity and functioning of the reverse transcription complex.

Although matrix is an essential component of retroviral and lentiviral genomes, Göttlinger and colleagues **(Abstract S40)** presented evidence that in a specific T-cell line, virus replication can occur in the complete absence of matrix protein provided that concomitant deletions in the transmembrane glycoprotein of envelope were present. If HIV cores were pseudotyped with VSV-G envelope, matrix appeared to be dispensable for replication in T cells. In contrast, matrix-deletion mutants were impaired in their ability to infect nondividing macrophages, consistent with studies invoking a role for matrix in translocation of viral reverse transcription complexes in nondividing macrophages.

Several investigators presented studies that shed new insight into the role of specific genomic RNA encapsidation that is mediated by nucleocapsid. Summers and colleagues **(Abstract S37)** examined the basis through which RNA encapsidation is mediated by a specific interaction between nucleocapsid and a stem loop structure (SL3) in genomic RNA (known as the *psi* site). The tight interaction between nucleocapsid and SL3 RNA (K_d = 50 nM) was shown to be mediated by a specific interaction between zinc finger motifs of the nucleocapsid protein and G^7 and G^9 nucleotide bases of the G^6-G^7-A^8-G^9 RNA tetraloop. The NMR structure of NC protein bound to SL3 provides new insight into the mechanism of genomic RNA recognition and encapsidation. The process of RNA encapsidation ensures not only that unspliced genomic RNA specifically is incorporated into virions, but also that 2 copies of genomic RNA are incorporated into each viral particle. Wainberg and colleagues **(Abstract 513)** examined the phenotype of viruses containing mutations in an RNA stem loop structure implicated in dimerization of viral RNA. Deletions in this RNA dimerization site compromised viral replication in vitro. Long-term culture led to the emergence of revertant variants containing mutations in Gag matrix, Gag p2, and Gag nucleocapsid proteins. These findings may underscore additional roles for Gag matrix and Gag p2 in mediating either incorporation or dimerization of genomic viral RNA during virus assembly.

Given the well-recognized ability of HIV-1 to infect nondividing cells, a number of investigators have begun to

exploit HIV-1-based lentivirus vectors as a tool to transduce nondividing target cells. Although HIV-1-based vectors efficiently transduce nondividing cells such as macrophages, resting T cells are refractory to infection both by wild-type HIV and HIV base vectors. Rate-limiting levels of dNTPs, which are the building blocks for cDNA synthesis, and inefficient nuclear targeting of viral DNA have been implicated in the resistance of resting T cells to HIV-1 infection.

Littman and colleagues **(Abstract 56)** demonstrated that resting T cells could be transduced with an HIV-1-based vector if the cells were cultured in the presence of cytokines such as IL-2, IL-4, IL-7, or IL-15. Although it is unclear how this cytokine stimulation overcomes the block to infection of resting T cells by HIV-1, this approach will prove useful in transducing primary lymphocytes with HIV-1 without the need for additional exogenous stimuli.

The theme of resting cell infection by HIV-1 was echoed by Haase and colleagues **(Abstract LB4)** who examined the phenotype of SIV- and HIV-infected T cells in vivo. Following intravaginal inoculation of monkeys with SIV, most of the viral RNA-positive cells were found to be T cells both at the site of inoculation and in lymphatic tissues after dissemination. Surprisingly, however, most of the infected T cells did not appear to be activated since they did not express HLADR, Ki67, or cyclin A. These nonactivated cells expressed less viral RNA than infected cells that exhibited activation markers. Over the course of infection, the proportion of cells that were infected and activated increased. These studies suggest that T-cell activation may not be an absolute requirement for productive infection of T cells in vivo. It remains to be determined whether the productively infected nonactivated T cells in vivo resemble the cytokine-stimulated resting T cells that are permissive to productive HIV-1 infection as described by Littman and colleagues **(Abstract 56)**.

Viral Tropism/Coreceptor Usage

Research carried out over the past year has begun to enforce the model that CD4 does not serve as a viral receptor per se but promotes conformational changes in envelope that confer competence for coreceptor binding. In addition, HIV-1 and HIV-2 variants that do not require CD4 for infection have been described. This would suggest that envelope glycoproteins of these viruses are already in the appropriate configuration for coreceptor binding. One model proposed to explain the adaptation to CD4 utilization by primate lentiviruses invokes an "immune cloaking" mechanism. Presumably, coreceptor binding epitopes represent targets for neutralizing antibodies. Thus, in an attempt to avoid exposure of these epitopes, the virus has evolved to use CD4 interaction to expose coreceptor binding epitopes immediately prior to infection of the cell. A prediction of this model is that viruses that infect cells by a CD4-independent mechanism and that presumably have consistently exposed coreceptor binding epitopes may be more sensitive to antibody neutralization.

Consistent with this prediction, Doms and colleagues **(Abstract S11)** examined neutralization sensitivity of an HIV-1 isolate (HIV-1 IIIB8X), which utilizes CXCR4 without the need for CD4. Doms presented evidence that this variant was approximately 1 log more sensitive to neutralization by sera from HIV-1 seropositive individuals. Replacement of the V3 loop of the CXCR4-utilizing 8X virus with the V3 loop of a CCR5-utilizing virus resulted in a chimeric variant that exhibited CD4-independent CCR5-dependent infection. Thus, the V3 loop confers coreceptor choice but does not impact CD4 dependence. These studies point to new strategies for development of antibodies that target coreceptor binding epitopes of envelope glycoproteins, a theme that was mirrored by a recent publication in Science that fusion complexes derived from HIV-1 envelope expressing cells elicit broadly neutralizing antibody responses **(*Science* 283: 357, 1999)**.

As coreceptor ligands, SDF-1 (CXCR4 ligand) and RANTES, MIP-1α, and MIP-1β (CCR5 ligands) have been shown to inhibit HIV-1 infection. Studies presented at the Conference **(Abstracts S12, S13)** demonstrated paradoxically that RANTES enhances infectivity of HIV-1 isolates via CXCR4 (X4 isolates). Trkola and colleagues **(Abstract S13)** describe the mechanism through which RANTES enhances virus infection. RANTES was shown to enhance not only HIV-1 infectivity but also the infectivity of other viruses such as vaccinia, influenza, VSV, and MLV. Thus, the RANTES enhancement effect appeared to be independent of the route of virus entry or of coreceptor usage. Two mechanisms of enhancement were suggested. The first involves a mechanism in which RANTES may induce signaling and alter permissivity of cells to virus entry. A second mechanism likely involves cross-linking of virions to cells through interaction of RANTES with glycosoaminoglycans on cell and viral membranes that could be inhibited by treatment of cells with chondroitin sulfate.

Gordon and colleagues **(Abstract 505)** echoed the finding that RANTES enhances viral infectivity by 2 mechanisms that are inde-

pendent of the mode of viral entry or coreceptor usage. Sodroski and colleagues **(Abstract S13A)** demonstrated that posttranslational modifications on CCR5 modulate the ability of these proteins to mediate HIV-1 entry. CCR5 was shown to be modified by O-glycosylation and by sulfation of its N-terminal tyrosines. Sulfated tyro-sines modulated the binding of CCR5 to MIP-1α and MIP-1β and to gp120/CD4 complexes. Mutation of a critical sulfated tyrosine impaired the ability of HIV-1 to enter cells via CCR5 and CD4. The authors suggested that differences in CCR5 sulfation between different cell types would impact on the ability of these cells to be infected by HIV via CCR5.

In approximately 50% of patients who progress to full-blown AIDS, there is an apparent switch in coreceptor usage in that viruses obtained late in disease exhibit CXCR4 (X4) tropism whereas viruses obtained early in disease exhibit predominantly CCR5 (R5) tropism. Studies presented at the Conference **(Abstract 521)** suggested that envelope sequences derived from HIV-1 isolates obtained from both brain and colon exhibited R5 usage, not X4 usage. Thus, in contrast to the frequently observed switch in coreceptor specificity in comparing blood-derived viruses early after HIV infected and after the onset of AIDS, CCR5 appeared to be a primary coreceptor for brain-derived and colon-derived viruses. Thus, tissue infection appears to select for CCR5 usage throughout disease progression.

HIV-1 infection of macrophages is mediated by CCR5. Thus, macrophages obtained from individuals with a homozygous deletion in CCR5 are resistant to infection by macrophage tropic HIV-1. It has also been established that while CXCR4 is expressed on macrophages, it is inefficiently utilized by X4 tropic viruses. Studies presented at the Conference **(Abstract 499)** further investigated the mechanism through which some X4 tropic viruses are able to utilize CXCR4 for infection of macrophages. The investigators analyzed a dual tropic isolate (DH12), which uses CCR5 and CXCR4 and which infects macro-phages from homozygous CCR5 deleted individuals. The investigators further compared macrophage infectivity by lab-adapted and primary isolates that exhibit X4 tropism. Primary HIV-1 isolates were able to infect macrophages via CXCR4, which is in contrast to lab-adapted strains that were not able to utilize CXCR4 for macrophage infection. Thus, the failure of lab-adapted isolates to enter macrophages through CXCR4 may be a feature of lab adaption and primary dual tropic viruses may exploit both coreceptors for macrophage infection. ■

Dr Stevenson is a Professor at University of Massachusetts Medical Center, Worcester, Massachusetts.

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ADVANCES IN THE UNDERSTANDING OF HIV PATHOGENESIS

Bruce D. Walker, MD

There has been an accelerated increase in our understanding of HIV pathogenesis in the past year, ranging from host to viral to immunologic factors. In the same way that the 1996 International AIDS Conference in Vancouver will be remembered for delivering stunning results with antiviral combinations including protease inhibitors, the 1999 Retrovirus Conference in Chicago will be remembered for numerous demonstrations on just how much the immune system contributes to control of viremia. The prospects of turning this knowledge into new intervention strategies affords room for great optimism.

HOST FACTORS IN HIV PATHOGENESIS

One of the most important questions surrounding HIV pathogenesis is why some persons progress rapidly while others progress slowly. It has long been speculated that genetic polymorphic HLA class I molecules may be involved because they present viral peptides to the immune system for recognition. Numerous previous studies have suggested that particular HLA class I alleles may be associated with greater risk of progression. In an extensive genetic analysis of persons from several longitudinal cohorts, O'Brien et al **(Abstract S14)** reported that individuals with greater heterozygosity in class I alleles fare significantly better. This seems reasonable, since more heterozygosity at class I alleles should allow for a more diverse array of epitopes to be presented. Coupled with other data showing the importance of cytotoxic T lymphocytes (CTL) in controlling viremia (see below), these studies suggest that prognosis may depend on the breadth of the immune response. In addition, these cohort studies revealed that certain HLA alleles are particularly associated with rapid disease progression, including Cw4 and B35. One possible conclusion of O'Brien's study and that of Kalsow et al **(Abstract 565)** is that the particular HLA alleles used to present epitopes may vary in their efficiency of presentation. Future analysis of the link between MHC alleles, immune responses, and disease course will be particularly important.

Advances in characterization of macaque MHC alleles and CTL responses may afford an animal model to help dissect these influences. Evans et al **(Abstract 255)** showed that MHC alleles are important in directing the CTL responses. Their studies indicate that more broadly directed responses appear to be associated with a better outcome and that considerable immune selection pressure is applied through these responses, with subsequent development of immune escape viral variants.

The Conference also featured additional data on the role of chemokine receptor polymorphisms in disease progression. The link between (32 CCR5 heterozygosity and slower disease progression was confirmed in adults and extended to children **(Abstract 269)**. Kostrikis et al presented data indicating that CCR5 polymorphisms may be related to the risk of maternal-fetal transmission **(Abstract 263)**. Paxton et al **(Abstract 258)**, testing pre-seroconversion blood samples, reported that higher levels of RANTES production by activated CD4+ cells but not CD8+ cells correlated with slower disease progression and lower viral loads at set point. Individuals heterozygous for the CCR5 delta 32 mutation had higher levels of RANTES production, offering an intriguing explanation for the slower disease progression in persons with this genotype. The potential role of the 3'A polymorphism in SDF1 (the chemokine ligand for CXCR4) on disease progression remains contested **(Abstracts 259, 568)**.

VIRAL FACTORS

There remains little doubt that viral attenuation can be associated with less rapid disease progression, and that attenuated strains of SIV can confer protection against challenge with pathogenic viruses. Understanding the immune responses that are operative in these animals is critical, and progress is being made. Nixon et al reported that better protection was achieved with longer duration between immunization and challenge (7 of 8 animals protected at 15 weeks versus 3 of 8 at 5 or 10 weeks), and strong CTL responses were detected in 2 of 3 protected animals that were studied **(Abstract 31)**. These data are consistent with previous reports, as was the finding that neutralizing antibodies did not appear to be correlated with protection.

An intriguing potential link between viral phenotype and pathogenicity was reported by Stoddart et al **(Abstract 4)**. They showed marked differences in thymic pathology when comparing protease inhibitor-sensitive with protease inhibitor-resistant viruses in a SCID-hu Thy/Liv mouse model. Protease inhibitor-sensitive clones of virus replicated to high levels in the thymus and caused T-cell depletion. The same virus with a

patient-derived protease resistance domain exhibited severely impaired thymic replication and did not cause T-cell depletion. This observed lack of viral fitness in vivo in primary lymphoid tissue is encouraging and could be invoked to help explain anecdotal reports of lack of expected disease progression in persons who have protease inhibitor-resistant virus and who continue on the therapy. However, since it has been shown in vitro that protease inhibitor mutations impair replicative capacity but that compensatory mutations in protease and gag cleavage sites restore more wild-type replication, more studies are clearly needed to determine the biologic significance of these findings.

Immunologic Factors

Not long ago a widely held view was that the immune system contributed little in the fight against HIV and SIV, which was supported by the demonstration that these viruses essentially represent infections of the immune system itself. From some of the most dramatic advances reported at the Conference, it is now clear that the immune system plays a major role in contributing to the viral set point. Moreover, the correlates of protective immunity, or at least those immune responses that are associated with control of viremia, are being better defined. In contrast to earlier Conferences in which the focus was on neutralizing antibodies, cellular immune responses took center stage at this year's Conference.

Advances in understanding the role of CTLs in HIV infection come in part from newer assay techniques involving direct visualization of CTL by flow cytometry using HLA-peptide tetramers, and in part from cohort studies of persons with long-term nonprogressing infection. The magnitude of the CTL response in acute infection is likely higher than previously appreciated **(Abstract 25)**, and additional data confirm the presence of a vigorous CTL response in persons who are controlling viremia without antiviral drug therapy **(Abstract 562)**. A potential reason for the lack of better efficacy of CTLs in vivo was provided by Andersson et al **(Abstracts 62, LB3b)**, who reported that CTLs found in lymph nodes contained granzyme but not perforin, leading the authors to conclude that these cells were not fully functional.

The critical role of CD8+ cells in controlling HIV replication was demonstrated in experiments involving in vivo depletion of CD8+ cells in SIV-infected macaques with a monoclonal antibody. Schmitz et al reported that transient depletion of CD8+ cells in either acutely or chronically infected animals resulted in dramatic increases in viral load, which subsequently declined as CD8+ cells returned **(Abstract 252)**. The rise in viremia also correlated with depletion of CTLs as determined by tetramer analysis. Similar results were reported by Xin et al, who concluded based on preliminary mathematical modeling that the changes in viremia could not be due to cytolysis alone, but might also include a soluble factor **(Abstract 253)**. This does not rule out that the effector cells are CTLs, since CTLs are known to inhibit viral replication by both cytolytic and noncytolytic mechanisms. Together these reports provide the strongest evidence to date that the cellular immune system is directly involved in the dynamic equilibrium at viral setpoint.

Further evidence for an antiviral role of CTLs was provided by Brodie et al **(Abstract 26)** in studies of adoptive transfer of CTL clones in infected humans. CTLs specific for Gag epitopes were infused and shown to migrate to sites of infected cells in lymphoid tissue. Moreover, the transfers were associated with transient decreases in peripheral blood mononuclear cell (PBMC) viral load. That the antiviral effect was not long-lived was speculated to be due to lack of sufficient CD4+ T-helper cell function, and future studies will need to address this issue. Clonal analysis of CTL responses in MHC-matched macaques also support an antiviral role for CTLs, since immune selection pressure by CTLs could be clearly demonstrated in this experimental infection **(Abstract 255)**.

That the cellular immune system plays a major role in HIV-1 infection should not be surprising based on animal models of chronic viral infections, as outlined beautifully by Ahmed in a plenary lecture **(Abstract L6)**. CTLs are clearly required to maintain control of viremia, and it is clear that these responses are critically dependent on CD4+ T-helper cells. Even transient depletion of CD4+ cells in murine lymphocytic choriomeningitis virus infection leads to impaired CTL responses and lack of control of viremia during the chronic phase of infection. New data in mice suggest that CTLs can exist in vivo in a nonfunctional state, and that this phenotype is more pronounced in settings of CD4+ T cell deficiency, as is seen with HIV and SIV infections.

Emerging data also extend the understanding of HIV-1-specific T-helper cell responses in HIV pathogenesis, but some controversies are emerging as additional data are generated. Numerous laboratories have now confirmed that Gag-specific T-helper cell responses are more robust in persons with nonprogressing infection **(Abstracts S41, S44, 23, 30, 562)**, and at least 2 labs have reported a strong negative correlation between viral load and Gag-specific T-helper cell responses **(Abstracts S41, S44)**. Although responses are lower in persons with chronic infection, a new and more sensitive assay described by Picker et al **(Abstract 27)**, which

relies on gamma interferon production assessed by flow cytometry, indicates that these cells may be present in chronic infection in greater numbers than previously anticipated. Binley et al **(Abstract 30)** reported no association between Gag-specific T-helper cell responses and viremia, using a slightly different assay technique. It remains to be determined whether stronger HIV-1-specific T-helper cell responses are causally related to lower viral loads in those studies in which this association has been observed.

The Special Case of the Exposed Seronegative Person

Historically, one of the major arguments used in favor of the immune system playing a major protective role has been the report of persons who have been heavily exposed to HIV and yet have remained seronegative. Investigators at previous Conferences have reported the detection of cellular immune responses in at least a subset of such persons who appear not to be infected, based on negative virus culture results, no detectable viral load, negative quantitative DNA PCR, and negative ELISA and Western blot tests. The finding of HIV-1-specific CTL and sometimes T-helper cell responses has raised the question of whether these persons might have cleared a transient or abortive infection. With the report of Zhu et al **(Abstract 8)**, it appears that at least some of these persons may actually harbor virus after all. Zhu et al performed an exhaustive analysis for HIV-1 DNA in a cohort of heavily exposed yet persistently seronegative persons at the University of Washington. They reported the persistent detection of gag, pol, and env sequences in such persons during a 2-year follow-up in which they remained seronegative. In a majority of persons studied, there was marked sequence homogeneity, and phylogenetic analysis revealed that the detection of HIV sequences was not due to laboratory contamination. In one individual low levels of sequence evolution were observed, suggesting persistent low-level virus replication. These very interesting results will need to be confirmed.

Immune Reconstitution

The final symposium of the Conference was devoted to the topic of immune reconstitution, and the data presented provided a degree of justified optimism for the future. The entire field of immune reconstitution has come of age with the advent of potent antiretroviral therapy. The ability to control viremia in newly infected infants has resulted in the ability to respond robustly to immunogens, providing hope that effective HIV-specific immune responses might be able to be induced with therapeutic vaccination **(Abstract L2)**. Prolonged therapy has already resulted in restoration of cytomegalovirus-specific (CMV) immune responses in adults **(Abstract 250)** and in reconstitution of MAC-specific immunity **(Abstract 248)**. These and other data **(Poster sessions 45 and 46)** provide hope that HIV-specific immunity might also be able to be induced with continued viral suppression. Although regeneration of HIV-specific immune function with antiviral therapy alone has been infrequent, the first reports of restitution of HIV-specific T-helper cells came to this meeting from Lori et al **(Abstract 401)**, in which 5 of 11 persons on prolonged didanosine/hydroxyurea therapy generated significant Gag-specific T-helper cell responses.

HIV clearly has a negative impact on the regenerative capacity of bone marrow and thymus **(Abstracts 22, S43)**. The fact that the thymus remains active well into adult life **(Abstracts 21, S42, S43)**, and that potent antiretroviral therapy results in increases in recent thymic emigrants **(Abstracts S42, LB1)**, suggests that prolonged therapy may result in repopulating with cells that may be able to be educated to mediate HIV-specific immunity. This notion is also supported by more extensive longitudinal data indicating that the fraction of naive cells continues to increase with prolonged antiviral therapy **(Abstracts S44)**.

One of the most fundamental questions related to the prospect for immune reconstitution has to do with whether the immune system can ever successfully control the virus. Data presented at this conference confirm that some individuals are able to control viremia in the absence of antiretroviral drug therapy, and that this occurs in the setting of strong virus-specific cellular immune responses **(Abstracts S41, 562)**. Furthermore, at least 3 groups reported that early intervention with potent antiretroviral therapy, particularly when instituted prior to seroconversion, is associated with the development of strong virus-specific T-helper cell responses **(Abstracts S41, S44, 23)**. The critical question of how long after seroconversion one can wait to initiate therapy and still see recovery of these responses remains to be answered. The fact that all persons treated prior to seroconversion had detectable responses **(Abstract S41)**, whereas these responses were less predictable in persons treated in the early stages of chronic infection, suggests that there may be better success with earlier therapy. However, any clinical benefit to patients from restoration or augmentation of these responses

remains to be determined.

These cases of early therapy resulting in the generation of potent antiviral immune responses raises the obvious question of whether these persons might be able to control viremia on their own in the absence of ongoing drug therapy. A corollary to this question is whether these more robust immune responses might allow the immune system to be more specifically boosted with some type of therapeutic vaccine. A number of anecdotal cases presented at the conference provide room for cautious optimism. The sentinel case of such potential immune control following early therapy was presented by Lori **(Abstract LB5)** and involved a patient in Berlin who stopped therapy intermittently over the first 6 months of treatment. At the first discontinuation approximately 1 month into therapy, viremia immediately recurred, but was controlled with reinstitution of drug therapy. On the second transient discontinuation of therapy approximately 2 months later, there was no documented rise in viral load. The patient finally discontinued therapy at 6 months and has now been followed up for an additional 24 months with continued plasma viral load levels of <1000 copies/mL. In this case, the low viral load is associated with persistent strong virus-specific T-helper cell and CTL responses, consistent with immune control of viremia. This case has suggested that early therapy, perhaps with immune boosting, might result in immune containment.

Additional anecdotal cases presented at the Conference further support the possibility that the immune system might be harnessed to contain HIV replication. Ortiz et al **(Abstract 256)** reported on 4 patients who discontinued therapy on their own; in 2, consistently low viral loads were maintained. These low viral loads were associated with strong and broadly directed CTL responses, whereas those persons who were unable to contain viral replication had narrower or absent virus-specific CTL. Neutralizing antibody responses and T-helper cell responses, which might be expected to play a role as well, are yet to be reported.

The possibility that immune control might be achieved following early therapy of acute infection is being tested in at least 1 clinical trial, with others undoubtedly on the way. Rosenberg et al **(Abstract S41)** intentionally discontinued therapy in a patient who had been treated for 17 months from the time of acute infection. Prior to stopping therapy, this person had strong virus-specific T-helper cell responses and strong CTL responses. Once therapy was stopped, virus slowly re-emerged but with kinetics that were much slower than previously observed in persons who discontinue therapy in chronic infection. Viral load was rapidly contained with reinstitution of therapy, and recently therapy was stopped for a second time in the same person to see if intermittent therapy can boost existing responses to some threshold needed for persistent control of viremia. The possibility that intermittent therapy might lead to enhanced immune responses was also suggested by data presented by Lori et al **(Abstract LB5)**, in which they observed a progressive delay in viral rebound with successive interruptions in therapy in person's started on therapy within a year of seroconversion. The theory being tested in both of these trials is that endogenous virus might be used as a vaccine. The availability of potent antiretroviral therapy allows the administration of somewhat regulated doses of a live replicating vaccine, namely the person's own endogenous virus. However, it is important to note that these trials are in their earliest stages and no conclusions can yet be made. It is important that such trials be conducted under very controlled circumstances, particularly given the fact that most persons with chronic infection who discontinue therapy will experience a high viral load.

Other attempts at immune reconstitution involved administration of IL-2, adoptive transfer of antigen-specific cells, and therapeutic vaccination. Chun et al report that 2 persons treated with prolonged courses of IL-2 in the context of potent antiretroviral therapy no longer had culturable virus, and they are discontinuing therapy on these persons to determine whether viremia will recur **(Abstract 496)**. Follow-up is as yet too short to draw conclusions. Hege et al **(Abstract 33)** are infusing genetically engineered cells that express a chimeric T-cell receptor comprising the extracellular portion of the CD4 molecule coupled to the T-cell receptor zeta chain, which allows for cells expressing this receptor to lyse gp120-expressing target cells. Virologic results from this trial are still awaited. Valentine et al **(Abstract 346)** reported follow-up data from Geneva on a cohort of persons given therapeutic immunization with an envelope-depleted whole inactivated virus vaccine. Astounding levels of virus-specific proliferative responses were observed in those receiving the vaccine compared with those who received adjuvant alone, demonstrating that infected persons can be induced to generate these responses. However, a clinical benefit from induction of these responses is yet to be shown and will require specifically designed trials that are likely to be conducted in the next year.

In addition to these investigations of adoptive therapy involving cellular immune responses, there were some studies examining the potential role of antibody responses in immune reconstitution. The hurdles faced in harnessing more potent neutralizing

antibody responses were well outlined by Sodroski in the opening session **(Abstract L1)**. In particular, many sites on the virus envelope are hidden from antibody-mediated immune attack by heavy glycosylation. Mascola et al **(Abstract 257)** reported that combinations of neutralizing monoclonal antibodies greatly enhance the antiviral effect achieved, and in the same way that combination antiviral therapy ushered in a new era in treatment, combining different neutralizing antibodies may afford significant advances in harnessing effective humoral immunity.

Viral Reservoirs

Any attempt to control viremia has to address the issue of latent viral reservoirs. Although it had earlier been suggested that viral eradication might be an achievable goal, data on numerous fronts suggest that this is not going to be readily achievable. A major question is whether, in fact, it is even necessary. It is clear that immune control of viremia in those few persons who are successfully controlling the virus without antiretroviral therapy is associated with the persistence of replication competent virus. In fact, it may be that some degree of viral turnover is required in order to maintain the strong cellular immune responses that are observed. Attempts to flush out persistent reservoirs have provided a mixed picture. Prolonged courses of IL-2 and potent antiretroviral therapy have been associated with the inability to culture virus in a subset of treated persons **(Abstract 496)**. It seems more likely that this strategy may have allowed for immune boosting with autologous virus induced to replicate from the IL-2-activated cells rather than actual elimination of infectious virus. An attempt to flush out latent virus from persistent reservoirs by anti-CD3-mediated activation of T cells resulted in significant toxicity that will severely limit this approach **(Abstract LB6)**. In fact, any approach that requires activation of 1 million uninfected cells to induce 1 infected cell is likely to cause significant toxicity. Other more targeted strategies are awaited.

Conclusions

Recent advances in understanding HIV pathogenesis now provide clear evidence for the tremendous potential of the immune system directed against this virus. The fact that some persons are able to control HIV replication in the absence of antiretroviral drug therapy has to be seen as tremendously positive, and provides substantial ground for optimism that an effective vaccine will ultimately become available. Given what we now know, it seems most likely that a vaccine that would attenuate the effects of infection is the most realistic short-term goal. Such a vaccine would have tremendous impact where the epidemic is spreading most rapidly and where antiretroviral drug therapy remains inaccessible. The coming year should provide important advances in understanding the immune parameters required for successful control of virus, and this should directly facilitate vaccine development. We are clearly making progress.

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Dr Walker is Associate Professor of Medicine at Harvard Medical School and Director of the Partners AIDS Research Center, at Massachusetts General Hospital, Boston.

COMPLICATIONS OF HIV DISEASE AND ANTIRETROVIRAL THERAPY

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

METABOLIC COMPLICATIONS

Metabolic complications of HIV infection were the topic of more than 30 abstracts and a state-of-the-art symposium at the Conference. Research in this area has focused on describing the different components of what may or may not be a single syndrome. Active areas of investigation include glucose metabolism (including the role of insulin resistance), lipoprotein changes (cholesterol and triglyceride elevations), and body fat redistribution (fat accumulation and peripheral fat wasting). There were some data presented on the incidence and prevalence of the abnormalities, analysis of risk factors for developing specific changes, and some early data on possible interventions and outcomes in patients taking antiretroviral drugs. Many of the studies were retrospective, uncontrolled, and lacked objective measures and hence are difficult to interpret or compare. However, there were several well-designed studies that serve to move this area of investigation forward.

In the state-of-the-art symposium on metabolic complications, Grunfeld reviewed data on lipid changes from before the protease inhibitor era **(Abstract S3)**. He reminded the audience that many of the changes we are seeing today are occurring on a background of metabolic disturbances that may be attributable to HIV infection itself. He cautioned that this must be kept in mind as we work to understand the mechanisms of metabolic perturbations and as new treatment strategies are evaluated.

Incidence and Prevalence

The incidence and prevalence of specific metabolic abnormalities in patients taking antiretroviral therapy (1994 to 1998) were described in a retrospective clinic-based study of 964 patients by Lee and Mathews from San Diego **(Abstract 644)**. No significant increases in random glucose levels were identified. Modest increases in total cholesterol values between 20 to 50 mg/dL and average increases in random triglyceride levels of 100 mg/dL were noted. Patients taking protease inhibitors did appear to be at increased risk for abnormalities compared with patients taking no therapy or compared with those taking nucleoside reverse transcriptase inhibitors (nRTIs) alone. Of additional interest in this study was the characterization of other known cardiovascular risk factors among the HIV-infected patients receiving care. More than 60% of patients in their clinic had a least 1 risk factor for cardiovascular disease, and 23% had 2 or more risk factors. These results highlight the importance of interventions to control known risk factors for cardiovascular disease, ie, smoking cessation, therapy for hypertension and diabetes, and interventions to reduce lipid levels.

Metabolic complications in children taking protease inhibitors have recently been recognized and were highlighted in a poster by Watson and Farley from Baltimore **(Abstract 435)**. Increases in cholesterol (34 mg/dL mean) and triglycerides were reported among 82 perinatally infected children (aged 6 months to 13 years) on protease inhibitor therapy. They were associated with use of each of the available protease inhibitors, were highest in children receiving a ritonavir and saquinavir combination, and appeared to be of the same order and magnitude as has been reported in adults.

Risk Factors for Metabolic Changes

Several groups attempted to identify risk factors for developing body shape changes and lipid abnormalities among patients taking antiretroviral therapy. Dieterich **(Abstract 674)** evaluated more than 700 patients receiving care and examined the association between the use of androgen and anabolic therapies and the risk of developing body shape changes. In this cross-sectional study, a high proportion of patients (56%) reported using anabolic or androgen therapy. "Lipodystrophy", defined visually, was noted in 7% of patients on these therapies, 5% of patients on testosterone, 16% on nandrolone, and 25% (1 of 4 patients) on growth hormone. More than half of the patients with clinical lipodystrophy had elevated cholesterol and triglyceride levels. The retrospective nature and visual definition of lipodystrophy used limit the conclusions that can be drawn. However, the low rates of lipodystrophy in patients taking androgens or anabolic therapy suggest prospective controlled trials are justified.

Carr and colleagues **(Abstract 641)** assessed the prevalence and severity of peripheral fat wasting and central obesity in a single practice setting using patient self-reports. Previous work by this group has demonstrated that self-report of body shape changes appears to correlate with some objective measures. In their study, only 17% of the patients denied any changes in body shape. The severity of body shape changes

noted by the participants appeared to correlate with total body fat. Retrospectively, they identified prior elevation in triglyceride levels and in C-peptide values as risk factors for body shape changes. These investigators postulate that early changes in triglycerides and C-peptide levels may be important in the pathogenesis of this syndrome.

A group of French investigators **(Abstract 642)** evaluated the frequency of lipodystrophy and attempted to characterize different variants of fat redistribution. They defined 3 clinical descriptions of body shape changes: lipoatrophic (71%), pseudo-obesity (62%), and mixed (46%). Among patients with each of these different types of body fat redistribution, the incidence of insulin resistance and glucose intolerance were comparable and occurred in about one third. Diabetes was rare and occurred in less than 10% of each of these groups. Elevated triglyceride levels (greater than 1.7 mg/dL) occurred in more than one third of patients. Elevations in cholesterol levels (greater than 6.7 mg/dL) occurred in more than 70% of patients in the 3 types. Among patients in their study who were taking protease inhibitors but did not develop 1 of the 3 fat redistribution patterns, the incidence of glucose intolerance and insulin resistance were significantly lower than the other groups. They concluded that diabetes, glucose intolerance, and insulin resistance appeared to be a significant feature of the syndrome, and that varied manifestations of body shape changes can occur during protease inhibitor therapy.

While most of the cohort studies that have examined the development of fat redistribution and lipid abnormalities have included men, at this year's Conference there was a poster session dedicated to the metabolic complications of antiretroviral therapy in women. Bausserman and colleagues **(Abstract 659)** evaluated 33 women taking protease inhibitors for a mean of 1 year and assessed body fat redistribution and insulin, glucose, and lipoprotein concentrations. In this study, two thirds of the women had an increase in waist-to-hip ratio above the 95th percentile for normal. Less evident were increases in cholesterol and triglyceride levels. Fasting glucose levels also appeared normal; however, 9 of the women had insulin levels above the normal range. Increase in waist-to-hip ratio appeared to correlate with elevation in triglyceride, lipoprotein B, and glucose and insulin levels. The results of this and other studies suggest that women are not spared the body shape changes. In another study by Currier and colleagues **(Abstract 663)**, rates of triglyceride and cholesterol elevations were examined among women enrolled in a prospective study of a regimen of nelfinavir/saquinavir/stavudine/lamivudine. No significant increases in triglyceride levels were noted in the women evaluated in this 48-week study; however, a small but statistically significant increase in cholesterol level (55 mg/dL) between baseline and follow-up was noted. Whether this increase represents high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol remains to be defined.

Data from the Women's Inter-Agency HIV study (WIHS) **(Abstract 661)** examined the association between diabetes and protease inhibitor therapy in women. After excluding women who reported pregnancy or a history of diabetes, they compared the development of diabetes in women based on the type of antiretroviral therapy they were taking. They identified a slight increase in the risk of diabetes in women who were taking protease inhibitors compared with other therapies, but no significant increase over HIV-seronegative women.

To date, most of the attention of metabolic and fat redistribution changes have implicated and focused on HIV protease inhibitors. Two groups reported on the development of body shape changes and lipid abnormalities in patients receiving nonprotease inhibitor-containing regimens. Saint-Marc **(Abstract 653)** described 17 patients with partial or generalized lipodystrophy who were on nRTIs alone for an average of 15 months. Of note, all of the patients in this series were taking stavudine in combination with lamivudine or didanosine. Fourteen of the 17 patients had low normal insulin levels, suggesting increased insulin sensitivity. They also reported that patients exhibited slight decreases in visceral adipose tissue, which is in contrast to what has been described in protease inhibitor-associated body shape changes. In the second report, Madge **(Abstract 654)** described 5 patients taking nRTIs with or without nonnucleoside reverse transcriptase inhibitors (NNRTIs) who developed changes in body shape. However, this study relied on patient self-report and lacked objective measures. Taken together with the published literature describing buffalo humps in patients prior to the availability of protease inhibitors, these reports remind us that factors other than protease inhibitors may be contributing to the development of body shape changes. The development of a consensus case definition for body shape changes would greatly strengthen the comparisons that can be drawn from these descriptive studies.

Interventions: Treat or Switch

Owing to the disfiguring effects of fat redistribution and the potential long-term complications of lipid abnormalities, investigators have begun to evaluate a variety of interventions targeted at patients taking

protease inhibitors who have metabolic complications and body shape changes. Several groups have focused on the role insulin resistance may play in the development of body fat redistribution and lipid abnormalities. One approach to increase insulin sensitivity is to use the drug metformin.

Saint-Marc and colleagues **(Abstract 672)** reported the preliminary results from a carefully designed and controlled study evaluating metformin in nondiabetic patients who had insulin resistance (fasting insulin concentration greater than 20 mUI/mL and central adiposity while taking protease inhibitor). After a screening period, patients underwent an 8-week observation period, followed by an 8-week double-blind, randomized period comparing metformin (800 mg orally three times a day) with no treatment. Fourteen patients were randomized to the metformin group and 13 to the no-treatment group. Objective measures of anthropometry and fat distribution were made using computed tomography (CT) scan, waist-to-hip ratio, height, weight, and bioimpedance assay. In addition, patients underwent oral glucose tolerance testing and had extensive lipid and endocrine profiles taken.

There was significant improvement in several parameters during the 8-week period of metformin treatment compared with the no-treatment group. Weight, fasting glucose level, and insulin levels fell significantly during this time. No significant difference was seen in total cholesterol or HDL or LDL cholesterol; however, triglyceride levels declined significantly over the treatment period. Visceral fat as measured by CT scan decreased by 37.5% in the metformin group and 10.4% in the no-treatment group. In addition, the ratio of visceral adipose tissue (VAT) to total adipose tissue (TAT) also declined significantly: 13.3% in the metformin group versus 5.7% in the control group. Waist-to-hip ratio also decreased significantly during the 8 weeks of metformin treatment. Metformin was well tolerated, although 2 patients were withdrawn due to gastrointestinal disorders including diarrhea and abdominal cramps. This study suggests that in a carefully selected group of patients with central adiposity, metformin is effective in restoring insulin sensitivity, reversing central adiposity, and lowering trigylceride levels over a short period of time. These results strengthen the hypothesis that insulin resistance may be one of the underlying mechanisms of the syndrome of central obesity and metabolic alterations complicating protease inhibitor-containing antiretroviral regimens.

Data using another drug that increases insulin sensitivity, troglitazone, were reported in 6 patients with diabetes mellitis and lipodystrophy who were taking protease inhibitor therapy **(Abstract 673)**. Patients were evaluated after 8 to 12 weeks of open-label therapy with troglitazone (400 mg/d). A decrease in fasting and postprandial glucose levels was observed. In addition, an initial rise in lipid values that later returned to baseline was noted. No definitive changes in body fat were demonstrated and no other laboratory abnormalities (specifically elevations in liver enzymes) were seen in this short period of follow-up. The role of troglitazone in nondiabetic, HIV-infected patients taking protease inhibitors remains undefined. The potential for hepatotoxicity and drug-drug interactions with protease inhibitors is likely to limit the use of this agent for managing metabolic abnormalities in HIV-infected patients.

Growth hormone has also been evaluated as a potential therapeutic option for body fat changes seen during protease inhibitor therapy. A noncontrolled study of 6 patients with established central obesity or buffalo hump evaluated the use of growth hormone therapy at a dose of 4 to 6 mg administered subcutaneously **(Abstract 675)**. Subjective improvement in the size and texture of the buffalo hump and central fat were noted; however, no changes in lipid profiles and no changes in fat wasting in the limbs were reported. The preliminary results of this study suggest that growth hormone may need to be combined with other agents if it is used in the therapy of fat redistribution.

The final strategy that was evaluated for the treatment of metabolic abnormalities associated with protease inhibitors was substitution of the protease inhibitor with an NNRTI. Four groups reported preliminary results from "switch" studies designed to evaluate the safety and efficacy of substituting an NNRTI for a protease inhibitor. The studies all enrolled patients who had sustained viral load levels below the limit of detection for at least 6 months on a protease inhibitor regimen. Three studies included only patients who had metabolic abnormalities or fat redistribution, and only 1 of these studies **(Abstract LB14)** had a randomized design. Carr **(Abstract 668)** reported that more than 20% of the patients (11 of 15) failed to maintain viral suppression below the limit of detection at 12 weeks after substituting nevirapine for a protease inhibitor. Moyle **(Abstract 669)** reported on the substitution of efavirenz for indinavir in patients who were clinically stable and had HIV RNA levels below 400 copies/mL of plasma. They noted a decrease in abdominal girth and an increase in weight after substituting the NNRTI; however, this was accompanied by the transient increase in

cholesterol that was reported to be caused by elevations in HDL. These changes appeared to return toward baseline between 12 and 24 weeks.

In the 1 randomized study reported, Ruiz presented preliminary data on 29 patients taking a stable protease inhibitor regimen who were randomized to receive either didanosine/stavudine/nevirapine or stavudine/lamivudine/protease inhibitor. After a follow-up period of 12 weeks, the patients randomized to the nevirapine arm had statistically significant declines in cholesterol and triglyceride levels and reported improved quality of life. In this preliminary report, no data on objective measures of fat redistribution were presented. Taken together, the data generated to date from these switch studies suggest that substituting an NNRTI for a protease inhibitor in patients with adequate viral suppression is associated with a small risk in viral rebound, and that over the short term body fat redistribution does not appear to resolve. Clearly, longer follow-up in controlled studies is needed to determine the safety and efficacy of this approach.

Long-Term Consequences and Strategies

The long-term consequences of the metabolic complications of HIV therapy have remained undefined. At this year's Conference, 3 groups attempted to quantitate the risk of myocardial infarction in patients with HIV infection who were taking protease inhibitors and nonprotease inhibitor-containing combinations and compare them with adults not infected with HIV **(Abstracts 656, 657, 658)**. Each of these series was limited by the small number of events and short follow-up time that resulted in wide confidence intervals; nevertheless, they found no statistically significant increase in risk of myocardial infarction in patients taking protease inhibitor regimens.

Specific guidelines for the management of lipid abnormalities in the setting of HIV infection have yet to be developed. In the interim, the use of the National Cholesterol Education Program (NCEP) Guidelines appears to be reasonable. Henry **(Abstract 671)** reported his clinical experience of following the NCEP guidelines for management of lipid abnormalities in patients with HIV infection. In 44 patients (48% of the patients taking protease inhibitors at their center), significant reductions in cholesterol and triglyceride levels were seen using diet and exercise as the initial intervention. Gemfibrozil was successful in lowering cholesterol by approximately 30% and triglyceride levels by 50 to 60% after 9 to 10 months of therapy. Atorvastatin was given to 21 patients, with significant improvements in both cholesterol and triglyceride levels and with no apparent toxic effect. Although further studies are still needed to quantitate the interactions between the cholesterol lowering drugs and protease inhibitors, the short-term data presented in this study should be viewed as reassuring news to clinicians.

Opportunistic Complications: Stopping Prophylaxis—How Safe Is It?

Just 3 years ago, a major focus of the annual Conference was on the optimal prophylactic regimens and strategies to prevent opportunistic infections. Guidelines were simple: When the CD4+ count drops below 200 cells/μL, start Pneumocystis carinii *pneumonia (PCP) prophylaxis; when the CD4+ drops below 50 cells/μL, start* Mycobacterium avium complex *(MAC) prophylaxis. There were no stopping rules, as continuing immune deterioration and hence a progressively increased risk for opportunistic infections were expected. Prophylaxis was for life. Potent antiretroviral regimens then became available, requiring consideration of these recommendations. Is PCP prophylaxis really necessary for patients in whom CD4+ cell counts have risen above 200 cells/μL as a result of potent antiretroviral therapy? Will cytomegalovirus (CMV) disease recur in patients treated with potent antiretroviral drugs who then discontinue CMV maintenance therapy? These questions and other related issues were addressed at this year's Conference. The discussion was not when to start prophylaxis, but rather, when to stop it.*

The rationale for stopping prophylaxis is supported by a series of observations first reported by Autran. She reviewed her extended observations in the Immune Reconstitution Symposium **(Abstract S44)**. While restoration of in vitro proliferative responses to HIV was limited, responses to pathogens (ie, CMV and *Mycobacterium tuberculosis* [TB]) were restored 3 to 6 months after starting highly active antiretroviral therapy (HAART), even in patients starting therapy with immune suppression. Koup and colleagues **(Abstract S42)** measured excisional DNA products of TCR-gene rearrangements and noted that potent antiretroviral therapy produced a rapid and sustained increase in thymic output. McCune **(Abstract S43)** provided further encouraging data showing that the fractional replacement rate of CD4+ cells is increased with potent antiretroviral therapy. For years, there had been a generally held belief that a decline of CD4+ cells below 50 cells/μL represented a "point of no return" in terms of immune recovery. Certainly, abundant laboratory data accumulated over the last few years and summarized in the immune reconstitution symposium argued to the contrary and supported

trials of discontinuation of prophylaxis.

The hypothesis that PCP prophylaxis could be safely discontinued in patients responding to potent antiretroviral therapy was tested in a randomized study presented by Lopez on behalf of a Spanish Collaborative Group **(Abstract LB7)**. The entry criteria for the study included a prior CD4+ cell count less than 200/μL or a history of PCP. All participants were taking PCP prophylaxis and potent antiretroviral therapy, and had a documented CD4+ cell count above 200/μL and HIV RNA level below 500 copies/mL for at least 3 months. Among the 332 patients followed up for a mean of 6 months, there were no episodes of PCP. Only 2 patients restarted prophylaxis. Of interest, 94% of patients had been taking trimethoprim/sulfamethoxazole, and no serious bacterial infections or toxoplasmosis cases were reported. Limitations of this study include the duration of follow-up to date and the small percentage (4% to 5%) with a history of prior PCP. Nevertheless, the results were supported by an observational study presented by Dworkin and colleagues from the Centers for Disease Control and Prevention (CDC) on the risk of PCP in patients who had a low CD4+ cell count and then responded to potent antiretroviral therapy **(Abstract 692)**. None of the subjects had received PCP prophylaxis after starting therapy, yet the risk of PCP was no different than that in a large group of subjects who never had CD4+ cell counts below 200/μL. These studies and 2 other observational studies presented previously by Furrer (Swiss Cohort Study **[Abstract 140]**) and by Reis (EuroSida **[Abstract 635]**) all suggest that discontinuation of PCP prophylaxis in HAART responders does not pose a significant risk.

The development of disseminated mycobacterial disease (DMD) in at-risk patients who responded to HAART was included in the analysis presented by Dworkin (692). Although this analysis included all DMD, the study addressed risk for MAC, which is the most common DMD. Data from more than 15,000 subjects in a large observational data base were incorporated, and demonstrated that risk for DMD was no different in a potent antiretroviral-treated group with a CD4+ count nadir below 50 cells/μL than in a control group without a CD4+ count value less than 100 cells/μL. With regard to MAC secondary prophylaxis or maintenance therapy in patients responding to potent antiretroviral therapy, investigators evaluated in vitro proliferative responses to MAC and gamma interferon production **(Abstract 248)**. In patients with a history of MAC who were currently taking potent therapy, cellular responses were of similar magnitude to healthy non HIV-infected controls, supporting attempts to discontinue MAC prophylaxis in this population.

Discontinuation of secondary prophylaxis for CMV has become common in patients who have responded to potent antiretroviral therapy. Support for this clinical practice was present in two observational studies, one described by Clotet on behalf of a Barcelona group **(Abstract 455)** and the other by Jouan on a cohort in Paris **(Abstract 456)**. No recurrence of CMV was noted in the 7 patients in the Spanish study who have been followed off prophylaxis for more than 2 years. In the French study, 2 cases of CMV developed among 47 subjects during the mean follow-up time of 7 months. One subject developed CMV in the ipsilateral eye (CD4+ count, 302 cells/μL) 11 weeks after stopping prophylaxis, and one subject developed presumed CMV neuropathy 6 weeks after stopping prophylaxis. In the patient with recurrent retinitis, in vitro proliferative responses to CMV present after potent antiretroviral therapy was started were absent at the time of relapse.

Torriani analyzed failures of CMV prophylaxis discontinuation in a San Diego cohort of 17 patients **(Abstract 250)**. The 5 subjects with recurrent CMV after stopping prophylaxis had CD4+ cell counts that had declined to below 50/μL (4 of 5), loss of HIV RNA suppression, and loss of in vitro proliferative responses to CMV. Reactivation occurred 8 days to 10 months after CD4+ counts dropped below 50 cells/μL and a median of 15 months after discontinuation of maintenance therapy. CMV retinitis recurred in a previously active zone of the retina in 4 of 5 patients, but contralateral eye involvement and disseminated disease occurred in 2 patients. This study emphasizes the point that when potent antiretroviral therapy fails, patients are at risk for recurrence of disease. When to restart prophylaxis for patients in whom virologic or immunologic failure occurs has now become a key clinical question, but it would seem risky not to reinitiate prophylaxis at a CD4+ count below 50 cells/μL.

MAC Treatment Options, More or Less

Although clarithromycin and ethambutol are considered the cornerstone of MAC therapy, the value of adding a third drug has not been established. The results of the ACTG 223, a MAC treatment trial conducted between December 1994 and June 1998 presented by Benson shed light on this issue **(Abstract 249)**. In this study, 160 patients with AIDS and MAC bacteremia were randomized to clarithromycin/ethambutol, clarithromycin/rifabutin, or clarithromycine/

thambutol/rifabutin. The primary study endpoint was bacteriologic response, defined as 2 negative blood cultures for MAC. Response rates were 51% in the 3-drug arm, 40% in the clarithromycin/ethambutol arm, and 42% in the clarithromycin/ rifabutinarm. Evaluation of bacteriologic response at later time points suggested the superiority of the 3-drug arm. Bacteriologic relapse was noted in 6% of patients in the 3-drug arm, 7% in the clarithromycin/ethambutol arm, and 24% in the clarithromycin/ rifabutin arm. A survival advantage was observed in the 3-drug arm, but was not easily explained by the available data. While the results of this study clearly support the 3-drug approach, Benson acknowledged that the benefits of adding rifabutin need to be weighed against the potential detrimental drug-drug interactions with antiretroviral therapy this regimen could produce.

Risk of CMV Disease in Protease Inhibitor-Treated Patients

Several studies have documented the profound decline in new cases of CMV as a result of the widespread use of potent antiretroviral therapy. Nevertheless, patients with extreme CD4+ cell depletion still develop this debilitating complication. The Spanish CMV-AIDS study team attempted to identify at-risk patients by conducting an observational, prospective study of patients with detectable CMV antibody who had less than 100 CD4+ cells/μL, and who were initiating protease inhibitor therapy **(Abstract 251)**. Among the cohort of 172 patients, 11% had CMV viremia (using a PCR-based assay) at baseline. CD4+ cell count and level of plasma HIV RNA was similar between CMV PCR-positive and -negative patients. The cumulative incidence of CMV disease was 6% at 2 years. CMV viremia was highly associated with development of disease (hazard, 4.4, 95% Confidence Interval [CI], 2.1-9.0). The event rate was 38% in CMV PCR-positive and 2% in CMV PCR-negative patients. All subjects with fewer than 50 CD4+ cells/μL at the start of therapy and greater than 1000 copies CMV/mL on the quantitative CMV PCR assay developed CMV disease. Consistent with previous observations, the majority (two thirds) of the new cases developed within the first 3 months of protease inhibitor initiation, suggesting pre-existing disease. These data argue strongly that a strategy utilizing "pre-emptive" therapy for CMV in high-risk patients merits attention and study. ■

Dr Havlir is Associate Professor of Medicine at the University of California San Diego

Dr Currier is Associate Professor of Medicine at the University of Los Angeles and Associate Director, UCLA Care Center

UPDATE ON DEVELOPMENTS IN ANTIRETROVIRAL THERAPY

Eoin P. G. Coakley, MD
Roger T. Inouye, MD
Scott M. Hammer, MD

Advances in antiretroviral chemotherapeutics were a dominant focus at the Conference. Within this rapidly expanding area, a number of major subtexts were highlighted at this year's meeting. These included (1) clinical trial results that described new options for initial therapy emphasizing protease inhibitor-sparing regimens; (2) new antiretroviral agents; (3) descriptions of the efficacy of a wide variety of combinations drawn from existing drug classes in antiretroviral-naive and -experienced individuals; (4) strategies of therapy including drug substitution and intensification; (5) new insights into viral resistance and its relevance for patient management; (6) drug activity in body compartments; (7) the utility of adjunctive agents such as interleukin-2 and hydroxyurea; and (8) immune reconstitution as a response to antiretroviral therapy. This review will summarize the major presentations in these areas.

OPTIONS FOR INITIAL THERAPY

Early trials of antiretroviral combination therapy confirmed the potency of triple-drug regimens consisting of a protease inhibitor with 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs) and rapidly established them as reasonable options for initial therapy. However, the demonstration of extensive cross-resistance between protease inhibitors and adverse effects such as lipodystrophy has led to concerns over the use of these drugs in initial therapy and a search for alternative initial regimens. Reflective of these concerns are the studies presented at the Conference that examined the efficacy and tolerability of alternative initial regimens containing a nonnucleoside reverse transcriptase inhibitor (NNRTI) with nRTIs and triple-nRTI combinations relative to a single protease inhibitor plus 2 nRTI triple-drug regimen.

NNRTI/2 nRTI Versus Protease Inhibitor/2 nRTI Regimens

DMP 266-006 study.– The potential for an NNRTI-based initial regimen to be a viable alternative to a protease inhibitor-based regimen as initial antitretroviral therapy, even at high plasma HIV-1 RNA levels, was suggested in a late-breaker presentation of the 48-week data from the DMP 266-006 study (Table 1) **(Abstract LB-16)**. In this Phase III, multi-center, open-label trial, protease inhibitor-, NNRTI-, lamivudine naive subjects (85% antiretroviral naive) were randomized to efavirenz/zidovudine/lamivudine; indinavir/zido-vudine/lamivudine; or efavirenz/indinavir. The efavirenz/zidovudine/lamivudine group had a statistically greater number of subjects (65%) in whom plasma viral RNA levels decreased to below the level of detection (<50 copies/mL) than the other 2 groups (44% and 47%, respectively, by intent-to-treat [ITT] analysis, non-completion equals failure [NC=F]). The virologic efficacy analysis was further stratified by baseline plasma HIV-1 RNA quartiles: <50,000; 50,000-100,000; 100,000-300,000; and >300,000 copies/mL. In an ITT analysis (NC=F) of the 48-week virologic data, the efavirenz/zidovudine/lamivudine group had a statistically significant increase in the percentage of patients in the highest and lowest quartiles in achieving plasma viral reductions to <400 copies/mL versus indinavir/zidovudine/lamivudine (P=0.01 and P=0.003, respectively) and overall was better tolerated **(Abstracts 382, 383)**. Because indinavir/efavirenz were not placebo-controlled, some of the "benefit" seen with the efavirenz-containing regimen in an ITT analysis might be attributed to a higher drop-out rate of patients in the indinavir-containing arms.

The Atlantic study.– Katlama et al reported the 24-week data from the Atlantic study (Table 1), a randomized, multicenter, open-label trial comparing indinavir/stavudine/didanosine with nevirapine/stavudine/didanosine or a triple-nRTI regimen, lamivudine/stavudine/didanosine **(Abstract 18)**. Participants were antiretroviral naive and had mean baseline plasma HIV-1 RNA level and CD4+ cell count of 4.22 $\log_{10}$ and 418/μL, respectively. In an ITT analysis (the corresponding "as treated" analysis data are noted in parentheses) after 24 weeks of therapy, 78% (83%) of the subjects in the indinavir-containing arm versus 67% (85%) of the nevirapine-containing arm and 56% (64%) of the triple-nRTI group had reductions in plasma HIV-1 RNA levels below 50 copies/mL. Furthermore, no significant differences in the initial HIV-1 clearance rates and lag-time were noted among the 3 study groups **(Abstract 634)**.

Triple-nRTI Versus Protease Inhibitor/2 nRTI Regimens

Abacavir-containing regimens.– Two studies were presented at the Conference that examined the efficacy and safety of a triple nRTI regimen con-

sisting of abacavir combined with zidovudine/lamivudine: CNA 3003 and 3005 (Table 1). The 48- week results from the CNA 3003 study were reported by Fischl et al **(Abstract 19)**. The safety and efficacy of abacavir/zidovudine/lamivudine were compared with zidovudine/lamivudine in 173 antiretroviral-naive patients with baseline median plasma HIV-1 RNA levels of 4.5 $\log_{10}$ and baseline CD4+ cell counts of 427-473/μL. Subjects were allowed to change to the open-label triple-drug combination at week 16 (70% of the original zidovudine/lamivudine recipients added other drugs). Of all patients receiving abacavir/zidovudine/lamivudine, plasma HIV-1 RNA levels were below 400 copies/mL in 61% and below 50 copies/mL in 56% at study's end. No difference was noted in virologic response between those individuals who initiated therapy with abacavir and those who added it subsequently. However, there was a negative correlation between a higher baseline viral load and the ability to attain a virologic response below the level of detection at 48 weeks. Similar to prior clinical trial experience, abacavir hypersensitivity was noted in about 2% of recipients.

In the CNA 3005 study, equivalent marker responses were demonstrated with a triple-nRTI regimen consisting of abacavir/zidovudine/lamivudine compared with indinavir/zidovudine/lamivudine in 562 antiretroviral-naive patients with baseline median-plasma HIV-1 RNA levels and CD4+ cell counts of 4.88 $\log_{10}$ and 360/μL **(Abstract 20)**. At week 24, each group had an approximate 2-$\log_{10}$ reduction in HIV-1 viremia and 65% had below 400 copies/mL (ITT analysis). Similar CD4+ cell responses were also noted at this time point (103/μL and 105/μL increases, respectively). To address the question whether a protease inhibitor-based regimen might be more effective at higher baseline viral loads, the data were analyzed for variation in virologic responses based on baseline plasma HIV-1 RNA levels of 10,000 to 100,000 and above 100,000 copies/mL. No significant differences were noted between the regimens at these 2 viral load strata except for a slight trend in favor of indinavir/zidovudine/lamivudine for up to 16 weeks. Abacavir hypersensitivity was reported in 5% of recipients.

New Investigational Agents

In addition to reports of the above-mentioned new combinations of more established antiretroviral drugs, data were presented on investigational compounds that continue to progress through more advanced stages of clinical testing or that show promising preclinical antiviral and pharmacokinetic properties.

Nucleoside Analogue Reverse Transcriptase Inhibitors

FTC.– Phase I/II FTC clinical trial data were presented by Delehanty et al **(Abstract 16)**. In this preliminary study of short-term 12-day virologic activity of this drug relative to lamivudine, 81 antiretroviral-naive patients were randomly assigned to either standard lamivudine dosing or FTC at 25, 100, or 200 mg administered once daily. Relative to the lamivudine study group, the FTC 200 mg group had significantly greater plasma HIV-1 RNA reductions from baseline levels of approximately 4.5 $\log_{10}$ by 1.45 and -1.70 $\log_{10}$, respectively (P=0.047). The rate of HIV-1 RNA reduction in this group was also significantly greater.

Other nRTIs.– Preclinical data from several other promising new nRTIs were presented including L-d4N analogues **(Abstracts 593, 597)**; BCH-10652 (dOTC), a cytidine analogue approximately 10-fold more potent than lamivudine and favorable pharmacokinetics **(Abstracts 595, 596)**; and a 5' hydrogen phosphonate zidovudine prodrug.

Nonnucleoside Reverse Transcriptase Inhibitors

Preclinical data were reported on several NNRTIs including AG1549 **(Abstract 12)**, DMP 961 and DMP 963 **(Abstract 13)**, GW420867X **(Abstracts 599, 600)**, and (-)calanolide B and (+)calanolide A **(Abstracts 602, 606)**. These compounds, in general, distinguish themselves from currently available NNRTIs with higher antiretroviral potency including, in some cases, activity versus strains with K103N as the key mutation and promising pharmacokinetic properties. AG1549, for example, is an NNRTI that exhibits low levels of protein binding and potent anti-HIV-1 activity (EC_{50} = 1.1 nM and EC_{90} = 3.4 nM) without substantial EC_{50}-fold increases to HIV-1 variants containing pivotal NNRTI-resistance mutations such as K103N, V106A, Y181C, Y188C, and P236L **(Abstract 12)**. High-level resistance, however, results from the presence of clusters of resistance mutations at positions 41, 62, 75, 77, 116, 151, 184, 103, and 181 (115-fold increase) and 41, 67, 69, 210, 215, 98, 181, and 190 (950-fold increase). Serial in vitro passage selects for 2 predominant genotypes: K103T/V106A/L234I and V106A/F227L.

Protease Inhibitors

ABT-378.– Marker efficacy data for the protease inhibitor ABT-378 pharmacokinetically enhanced by ritonavir (a potent inhibitor of ABT-378 metabolism) was presented by Murphy et al for the M97-720 Study Group (Table 1) **(Abstract 15)**. In this

Table 1. Trials in Antiretroviral-Naive Patients

Study Name (abstract number)	Regimen/Study Arm	Number of Patients	Duration of Therapy (weeks)	Baseline Plasma HIV-1 RNA (log_{10})	Baseline CD4+ (cells/μL)	Plasma HIV-1 RNA Change (log_{10}) or number (copies/mL)	CD4+ Change (cells/μL)	Comments
M97-720 **(15)**	ABT-378/ritonavir	101	24	4.8	399	93% and 95% of Group 1 and 2 with < 400copies/mL, respectively (observed)		ABT-378 administered at 200/100 mg or 400/100 mg bid (Group 1) or 400/100 mg or 400/200 mg bid (Group 2) Most common adverse effects: diarrhea, nausea; increased cholesterol in approximately 10%
CNA 3003 **(19)**	abacavir/zidovudine/ lamivudine	164	48	4.5	450	61% < 400 copies/mL 56% < 50 copies/mL	158	Baseline plasma HIV-1 RNA predicted 48 week virologic response
CNA 3005 **(20)**	abacavir/zidovudine/ lamivudine indinavir/zidovudine/ lamivudine	562	24	4.88	360	-2 -2		No difference in response between the abacavir- and indinavir-containing arms when baseline plasma HIV-1 RNA stratified to 10,000-100,000 and >100,000 copies/mL
HIV NAT 003 **(623)**	zidovudine/lamivudine/ didanosine zidovudine/lamivudine	106	48	3.83	340 (mean)	-1.23 -0.87	118 73	Significant difference between CD4+ cell changes (P<0.05)
Virgo I **(632)**	nevirapine (bid)/stavudine/ didanosine	60	52	4.51	415	-2.16	209 (+121 naive T-cells)	At 36 weeks, 76% <50 copies/mL; 5/6 patients with baseline plasma HIV-1 RNA >100,000 copies/mL with <50 copies/mL virologic response.
Virgo II **(632)**	nevirapine (qd)/stavudine/ didanosine	30	24	4.53	412	-2.53	140	At 24 weeks, 83% <50 copies/mL
M/3331/ 0013C **(624)**	delavirdine/zidovudine/ lamivudine zidovudine/lamivudine	152	54	5.33 5.27 (mean)	185 209	-1.9 -1.3	120 60	Rash seen in 36% of patients in the delavirdine arm
Ozcombo I **(633)**	indinavir/zidovudine/lamivudine indinavir/stavudine/lamivudine indinavir/stavudine/didanosine	109	52	5.08 (mean)	289 (mean)	-2.14 -2.59 -2.16	122 141 116	No difference between the virologic and immunologic responses of the 3 groups (P=0.11 and P=0.35, respectively)
DMP 266-003 **(383)**	efavirenz/indinavir	59	60	5.11 (mean)	282 (mean)	70% <50 copies/mL		Approximately 70% of patients decreased plasma HIV-1 RNA levels to <50 copies/mL from baseline plasma RNAs < and >100,000 copies/mL
DMP 266-020 **(383)**	efavirenz/2 nRTIs	92	48	4.32 (mean)	320 (mean)	36% <50 copies/mL		Approximately 36% of patients decreased plasma HIV-1 RNA levels to <50 copies/mL from baseline plasma RNAs <and> 100,000 copies/mL
DMP 266-006 **(LB-16)**	efavirenz/zidovudine/lamivudine indinavir/zidovudine/lamivudine efavirenz/indinavir	154* 148* 148*	48	4.77	348	65% <50 copies/mL 44% <50 copies/mL 47% <50 copies/mL		*Patients were protease inhibitor, NNRTI, lamivudine naive (85% were anti-retroviral naive). Intent-to-treat analysis (NC=F).CNS adverse effects observed in approximately 50% of efavirenz recipients. Efavirenz/zidovudine/lamivudine with significantly higher numbers of patients with week 48 HIV1RNA levels <400 copies/mL versus indinavir/zidovudine/lamivudine stratified by baseline viremia (<50,000 and >300,000 copies/mL) (P=0.01 and P=0.03, respectively).
Atlantic **(18)**	indinavir/stavudine/didanosine nevirapine/stavudine/didanosine lamivudine/stavudine/didanosine	300	24	4.22 (mean)	418 (mean)	71% <50 copies/mL 67% <50 copies/mL 56% <50 copies/mL		Intent-to-treat analysis
Atlantic **(631)**	ritonavir/indinavir/2nRTIs	67	24	5.32	227	67% <80 copies/mL		Adverse effects: mild diarrhea, nausea, and elevated triglycerides
IRIS **(630)**	ritonavir/saquinavir/ 1 nRTI indinavir/2 nRTIs	80 77	52	5 5.2 (mean)	213 243 (mean)	-2.4 -2.4	123 178	No significant differences in virologic or immunologic responses. Intent to-treat analysis
IRIS **(393)**	ritonavir/nelfinavir	20*	48	4.5	323	4/12 patients <20 copies/mL		*Half of patients nRTI protease inhibitor naive. Adverse effect: diarrhea. No consistent resistance genotype selected by ritonavir/nelfinavir.
SCAN **(628)**	nevirapine(qd)/stavudine/ didanosine nevirapine(bid)/stavudine/ didanosine	33 34	24	>5000	>500	-1.6 -1.7	148 102	No significant differences in virologic or immunologic responses (P=0.53 and P=0.60,respectively).
SCAN **(626)**	abacavir/amprenavir	11	72	4.42	756	72% <50 copies/mL 54% <5 copies/mL	175 naive T-cells	Most common adverse effect: nausea.
CNA 2004 **(625)**	abacavir/protease inhibitor (amprenavir, indinavir, nelfi-navir, ritonavir, or saquinavir)	82	48	4.78	349	44-60% <50 copies/mL		3% of patients with abacavir hypersensitivity. Of subjects with plasma HIV-1 RNA levels >400 copies/mL at week 16, 7 of 15 had protease mutations and 3 of 15 had an M184V abacavir mutation **(Abstract 115).**
Merck 035 **(388)**	indinavir/zidovudine/ lamivudine	33*	148	4.62	133	65% <50 copies/mL	>200	Intent-to-treat analysis. Adverse effects: nephrolithiasis and lipodystrophy in 38% and 19%, respectively.* Patients were zidovudine-experienced.
TRI-003 **(LB13)**	T-20 with a stable antiretroviral background	78	4	5.02	96			*Transient -1.5 log_{10} decrease in plasma HIV-1 RNA

clinical trial, approximately 100 antiretroviral-naive subjects were randomly assigned to 1 of 2 comparative dosing groups of: 200/100 mg bid or 400/100 mg bid combination of ABT-378/ritonavir (group 1) or a 400/100 versus 400/200 mg combination (group 2), respectively, in combination with stavudine/lamivudine in group 2. At baseline, participants had median plasma HIV-1 RNA levels of 4.8 $\log_{10}$ and CD4+ cell counts of 400/μL. By week 24, more than 90% of patients had plasma viral levels below 400 copies/mL in both treatment groups, and 89% of group 2 had reductions to below 50 copies/mL.

Data on other promising protease inhibitors in development were also presented including AG1776 **(Abstract 11)** and BMS-232632 **(Abstracts 603, 604)**.

Novel Agents

Fusion and cell entry inhibitors. In addition to advances in more established antiretroviral therapy that target the HIV-1 reverse transcriptase and protease, several groups at the Conference reported preclinical and clinical data characterizing the antiviral activity of compounds designed to disrupt other HIV-1 replicative functions, most prominently, HIV-1 cell fusion and entry **(Abstracts 608-618, LB13)**. In the late-breaker session, for example, Eron presented results from TRI-003, a multicenter, open-label Phase II clinical trial of T-20, a 36-amino-acid-peptide HIV gp-41-mediated fusion inhibitor (Table 1) **(Abstract LB13)**. Seventy-eight patients with either stable or no antiretroviral therapy (99% were antiretroviral experienced) and baseline plasma HIV-1 RNA levels and CD4+ cell counts of 5.02 $\log_{10}$ and 96/μL, respectively, were randomized to T-20 administered either by continuous or twice-daily subcutaneous injections. Over the 28-day study period, adequate trough levels were maintained with the twice-daily dosing schedule. Although viral rebound toward baseline was noted, within the first months of therapy, a transient 1.5-$\log_{10}$ reduction in viremia was observed. Genotypic analysis of these viral isolates showed mutations in the gp41 target site of T-20 at amino acid residues 36, 32, 38, and 39 **(Abstract 611)**. In general, the regimen was well tolerated.

Combination Regimens

Numerous clinical trials were reported that studied the virologic and immunologic profiles of rapidly increasing permutations of potent antiretroviral combinations, compared streamlined dosing schedules to standard regimens, and examined marker efficacy of combination regimens in specific clinical scenarios (Table 1).

Primary HIV-1 Infection

Prompted by recent immunologic studies that suggest that without antiretroviral therapy initiation early in HIV-1 infection there may be a loss of HIV-1 specific immune response, studies were presented that examined the efficacy of potent combination therapy started during primary HIV-1 infection.

One such study was reported by Markowitz et al **(Abstract 636)**. This was a 3-year follow-up of 38 newly infected patients who took protease inhibitor-containing combination therapy (ritonavir, indinavir, or ritonavir/saquinavir with 2 nRTIs) **(Abstract 636)**. All of these subjects had HIV-1 viremia reduced to below 500 copies/mL by 4.5 weeks and to below 400 copies/mL by 7.1 weeks. Of the 27 subjects remaining on study, 20 continued to have plasma HIV-1 RNA levels below 50 copies/mL and 7 had intermittently detectable viremia from a baseline mean of 309,832 copies/mL. Of 9 individuals with maximally suppressed HIV RNA, 7 had no detectable follicular dendritic cell-associated virus.

Soravia-Dunand et al also reported a primary HIV-1 infection therapeutic trial, in which indinavir/zidovudine/lamivudine was used in a multicenter, open-label observational fashion in patients presenting with acute HIV-1 infection (mean time from onset of symptoms to treatment was 29 days) **(Abstract 637)**. Subjects had a baseline mean plasma HIV-1 RNA level of 5.2 $\log_{10}$ and CD4+ cell count of 565/μL. At 24 months, the mean reduction in plasma viral levels was 2.1 $\log_{10}$ and mean CD4+ cell count was approximately 750/μL.

A third trial described by Kost et al employed a combination regimen of amprenavir/abacavir/zidovudine/lamivudine in recently (<90 days) infected HIV-1 patients **(Abstract 639)**. At 1 year, 7 of 9 patients had sustained plasma HIV-1 RNA levels below 50 copies/mL from a baseline mean of 156,725 copies/mL. Coincident mean CD4+ cell increases were 197/μL from a baseline of 610/μL. At week 26, naive CD4+ cells increased by a mean of 81/μL.

Therapy in Antiretroviral-Naive Patients: Protease Inhibitor-Containing Regimens

Indinavir/2 nRTI regimens.– The purpose of the Ozcombo I Study, reported by Carr et al, was to assess potential differences in marker efficacy between regimens containing indinavir paired with 3 different dual nRTI combinations including zidovudine/lamivudine, stavudine/lamivudine, and stavudine/didanosine **(Abstract 633)**. In this clinical trial, 109 antiretroviral-naive subjects with

mean baseline CD4+ and plasma HIV-1 RNA levels of 289/μL and 5.08 $\log_{10}$, respectively, were randomized to 1 of the 3 treatment groups. After 52 weeks of therapy, there were no statistically significant differences in virologic or immunologic response or in serious adverse effects among the study arms (Table 1).

Ritonavir/nelfinavir.– Gallant et al presented a 20-patient Phase II study evaluation of the marker efficacy and safety of a dual protease inhibitor (ritonavir/nelfinavir) (Table 1) **(Abstract 393)**. This open-label, multiple-dose trial enrolled protease inhibitor-naive patients (with a median baseline plasma HIV-1 RNA and CD4+ cell count of 4.5 $\log_{10}$ copies/mL and 323/μL, respectively. Ritonavir, 400 mg every 12 hours, was combined with either nelfinavir 500 mg (cohort I) or 750 mg (cohort II) every 12 hours, utilizing ritonavir's ability to enhance the pharmacokinetics of both nelfinavir and its metabolite, M8. After 48 weeks of therapy, the respective mean plasma HIV-1 RNA reductions and CD4+ cell increases in cohorts I and II were 2.82 and 2.21 $\log_{10}$ and 236 and 120/μL, respectively. Of the 12 patients completing this treatment duration, 4 had viral load levels below 20 copies/mL. Diarrhea was the most common adverse effect.

Ritonavir/indinavir.– In a study presented by Rockstroh on behalf of the German Ritonavir/Indinavir Study Group, 67 antiretroviral-naive recipients of these protease inhibitors combined with 2 nRTIs (predominantly zidovudine/lamivudine)resulted in the diminution of median baseline HIV-1 RNA levels from 5.32 to 1.90 $\log_{10}$ by week 24 (Table 1) **(Abstract 631)**. Of the patients analyzed at that time, 67% decreased plasma viral levels to below 80 copies/mL. In the same period, CD4+ cell counts increased from a baseline median of 227 to 424/μL. Ritonavir combined with indinavir, akin to ritonavir administered with nelfinavir, results in favorable pharmacokinetic interactions and allows for a twice-a-day dosing schedule and administration with food **(Abstracts 362, 363)**.

Protease Inhibitor/ Abacavir Combinations

Amprenavir/abacavir.– The recently approved 2' deoxyguanosine analogue reverse transcriptase inhibitor, abacavir, has been studied in combination that several protease inhibitors. Mellors et al presented updated data from the CNA 2004 study that examined the activity of abacavir administered with the 4 approved protease inhibitors as well as amprenavir in 82 antiretroviral-naive subjects with a baseline plasma HIV-1 RNA level of 4.78 $\log_{10}$ and CD4+ cell count of 349/μL **(Abstract 625)** (Table 1). At 48 weeks, between 44% and 60% of subjects (ITT analysis) had plasma HIV-1 levels below 50 copies/mL. As with previously reported results from this study, there were no statistically significant differences in marker efficacy between the abacavir/protease inhibitor dual regimens.

Updated data on the efficacy of amprenavir/abacavir were reported by Bart et al **(Abstract 626)** (Table 1). Of the 11 patients followed up for 72 weeks, 77% and 54% (ITT analysis) had plasma HIV-1 RNA levels reduced to below 50 and 5 copies/mL, respectively, from a baseline mean value of 4.42 $\log_{10}$. CD4+ cell counts increased to a mean of 974/μL from a baseline of 756/μL. A more detailed immunologic week-72 examination revealed an average increase of naive memory cells of greater than 150/μL and a statistically insignificant difference in CD4+:CD8+ lymphocyte ratios in lymph nodes between week 72-treated patients and HIV-1 seronegative controls.

NNRTI-Containing Regimens

Efavirenz-containing regimens.– In addition to the DMP 266-006 study discussed above, other studies were presented that examined the efficacy of efavirenz-containing combinations as initial antiretroviral therapy. Manion et al reported the results of post-hoc subgroup analyses on data from the DMP 266-003, -006, and -020 trials in order to determine the efficacy of these regimens in HIV-infected individuals with high baseline viral loads (ie, >5 $\log_{10}$ copies/mL) **(Abstract 383)** (Table 1). In the week 60 evaluation of the DMP 266-003 study, antiretroviral-naive recipients of efavirenz/indinavir with baseline plasma HIV-1 RNA levels above and below 5 $\log_{10}$ had comparable (approximately 70%) percentages of subjects in whom their viral loads were decreased to below 50 copies/mL (ITT, analysis NC=F). Similarly, in DMP 266-020, at week 48, approximately 36% of subjects from both baseline viral load strata had below <50 copies HIV RNA/mL plasma of detection on efavirenz/indinavir/nRTI (ITT, analysis NC=F).

Nevirapine/2 nRTI regimens.– Among the several clinical trials presented at the Conference that employed nevirapine plus 2 nRTIs as initial antiretroviral therapy was the Virgo Trial, which examined stavudine/didanosine once daily/nevirapine once or twice daily in 60 antiretroviral-naive subjects with median plasma HIV-1 RNA levels of 4.51 $\log_{10}$ and CD4+ cell count of 415/μL (Table 1) **(Abstract 632)**. In an ITT analysis at week 52 of stavudine/didanosine/nevirapine twice-daily therapy (Virgo I), 79% had plasma viral levels reduced to

Table 2. Trials in Antiretroviral-Experienced Patients

Study	Abstract Number	Prior Experience	Regimen/Study Arm	Number of Patients	Baseline HIV-1 RNA (median $\log_{10}$ copies/mL)	$CD4_+$ Count (cells/μL)
ACTG 370	488	(stavudine or didanosine)/ lamivudine	zidovudine/lamivudine/indinavir zidovudine/delavirdine/indinavir	33 30	3.6 3.5	90 80
Merck 035	388	zidovudine	indinavir/zidovudine/lamivudine	30	4.6	133
TIDBID	390	nRTIs	saquinavir (tid)/2nRTIs saquinavir (bid)/2nRTIs saquinavir(bid)/nelfinavir(bid)/ 1nRTI	47 39 47	*4.7 *4.7 *4.7	*312 *359 *334
SPICE	389	nRTIs	saquinavir (tid)/2 nRTIs nelfinavir (tid)/2 nRTIs saquinavir (tid)/nelfinavir (tid)/ 2 nRTIs saquinavir (tid)/nelfinavir (tid)	12 12 24 24	4.7 – 7.8	300 – 334
ACTG 364	489	nRTIs	nelfinavir/nRTIs efavirenz/nRTIs nelfinavir/efavirenz/nRTIs	66 65 64	3.9 3.9 3.8	384 385 397
ACTG 372B	490	nRTI/indinavir Salvage	adefovir/efavirenz/abacavir/nelfinavir adefovir/efavirenz/abacavir/nelfinavir placebo adefovir/efavirenz/nRTIs/nelfinavir adefovir/efavirenz/nRTIs/nelfinavir plc.	24 26 21 23	4.2 4.6 4.7 4.5	182 194 164 233
AG 1343-511/506	392	nRTI/nelfinavir Salvage	stavudine/lamivudine/ritonavir/ saquinavir	26	4.7	222
CNA 2007	133	nRTI/NNRTI/ protease inhibitor Salvage	abacavir/efavirenz/amprenavir	101		
Salvage	140	nRTI/protease inhibitor (minimal NNRTI) Salvage	nelfinavir/saquinavir/nRTIs nelfinavir/nRTIs nelfinavir/nRTIs/NNRTI	62	5.16	133

* Median CD4 and $\log_{10}$ HIV RNA values represent those for the study as a whole

Follow Up (weeks)	Plasma HIV-1 Change of % of Patients below Detection	CD4+ Change (median cells/μL)	Comments
20 – 24	42% <50 copies/mL 67% <50 copies/mL	80 – 100 80 – 100	Differences in outcomes did not reach statistical significance. Statistically significant incidence of hyperbilirubunemia in indinavir/delaviridine arms. Indinavir dosed at 600 mg q8h in indinavir/delaviridine-containing arms
148	66% <50 copies/mL	198	8/9 virologic failures had multiple RT + protease mutations 1/9 failed at 16 weeks with only M184V (RT) and L63P (protease) 13 (39%) subjects had 1 or more episodes of nephrolithiasis 4/21 met the clinical definition of lipodystrophy
32	32% ITT, (60%, OT) <50 copies/mL 20% ITT, (35%, OT) <50 copies/mL 35% ITT, (65%, OT) <50 copies/mL	175 150 160	For the study as a whole diarrhea was more frequent in the 2 protease inhibitor-containing arms (14% vs 8-9%)
72	33% <50 copies/mL (ITT, M=F) 25% <50 copies/mL 46% <50 copies/mL 21% <50 copies/mL	*200 – 300	The incidence of diarrhea was greatest in the 2 protease inhibitor arms
40 – 48	35% <500 copies/mL 60% <500 copies/mL 74% <500 copies/mL	94 94 94	3-way *P* value=0.001 for virologic outcome RT genotyping (n=146) revealed a median of 3 mutations/isolate. Virologic failure was significantly associated with prior lamivudine experience (OR, 5.2), baseline HIV-1 RNA level (OR, 2.4/log) and the number of RT mutations (OR, 1.3/mutation)
16	45% and 24% <500 copies/mL for NLV versus nelfinavir placebo, respectively (*P*=0.046) 37% and 32%,<500 copies/mL for abacavir versus nRTIs, respectively, (*P*=0.62)	60 14 36 36	CNS symptoms, rash and grade 2+ proteinuria were observed in 18%, 6%, and 17% of all subjects, respectively.
60	58% (LOCF)	120 (48 weeks)	21/26 subjects were multiply nucleoside experienced. Baseline viral load >30,000 copies/mL associated with virologic failure (*P*=0.03). Mutations at protease codons 48, 54, 82 and 84 not present at baseline. At baseline the presence of mutations D30N, L90M, M36I, or N88D was not correlated with virologic outcome at 48 weeks.
16	Of the 1st 65 subjects to reach 16 weeks, 34% had 1 $\log_{10}$ or greater decline in plasma RNA or <400 copies/mL RNA in plasma		Baseline factors associated with virologic failure included higher baseline viral loads, (*P*=0.0005), phenotypic resistance to efavirenz (*P*=0.006) or to abacavir (*P*=0.006), and the following RT mutations >2 zidovudine-associated mutations, T69D, Q151M complex, 68-69 insertion variants and NNRTI mutations Protease genotype at baseline was not predictive of virologic outcome
12	3% <400 copies/mL		At baseline the total number of protease inhibitor + RT mutations was the only factor significantly predictive of failure

below 500 copies/mL and CD4+ cell counts increased by 209/μL. Using the same regimen except with nevirapine dosed once a day (Virgo II), plasma HIV-1 RNA levels were reduced to below 500 copies/mL in 79% of cases by week 24. Coincident total CD4+ cell count increases were approximately 140/μL. Similarly, the Spanish Scan study, reported by Garcia et al, examined the virologic utility of stavudine/didanosine combined with either nevirapine dosed twice daily or once daily in antiretroviral-naive patients and found no statistically significant differences among the plasma HIV-1 RNA, CD4+ cell count, or tolerability between the 2 nevirapine dosing study groups (Table 1) **(Abstract 628)**.

Delavirdine/2 nRTI regimens.– Wood et al reported the results of M/3331/0013C, a placebo-controlled clinical trial comparing delavirdine/zidovudine/lamivudine and zidovudine/lamivudine in antiretroviral-naive subjects with mean baseline marker levels depicted in Table 1 **(Abstract 624)**. In on-treatment analyses, both virologic and immunologic responses at week 54 in the delavirdine/zidovudine/lamivudine group were significantly improved over the dual nRTI arm with mean CD4+ cell counts increasing by 120/μL (versus 60/μL) and plasma HIV-1 RNA levels reduced by 1.9 $\log_{10}$ (versus 1.3 $\log_{10}$). In a 24-week ITT analysis of virologic response according to baseline plasma HIV-1 RNA levels (<100,000 or >100,000 copies/mL), 68% of delavirdine/zidovudine/lamivudine recipients had <400 copies HIV RNA/mL plasma in the former group and 52% in the latter higher viral load group.

Clinical Trials in Antiretroviral-Experienced Patients

nRTI-Experienced subjects

Indinavir/2 nRTIs.– The 148-week follow-up of the Merck 035 study was presented in which 33 highly zidovudine-experienced subjects were treated with standard doses of indinavir, lamivudine, and zidovudine (Table 2) **(Abstract 388)**. The median baseline HIV-1 RNA level and CD4+ cell count were 4.6 log10 copies/mL and 133/μL, respectively. Prior to week 148, 11 subjects withdrew from the study; 7 because of viral rebound and 3 because of nephrolithiasis. At week 148, by ITT analysis with last observations carried forward (LOCF), 20 of 30 (66%) evaluable subjects had plasma HIV-1 RNA values <50 copies/mL with a median increase in CD4+ cells of 198/μL from baseline in these 30 subjects.

Saquinavir/nRTIs (+/-nelfinavir).– In this multicenter, randomized, open-label trial, saquinavir soft gelatin capsule (saquinavir-SGC) was administered at 1200 mg tid with 2 nRTIs (arm I); at 1600 mg bid with 2 nRTIs (arm II); or at 1200 mg bid with nelfinavir 1250 mg bid and 1 nRTI (arm III) (Table 2) **(Abstract 390)**. At baseline, the mean plasma HIV-1 RNA level was 4.7 $\log_{10}$ copies/mL and the mean CD4+ cell counts ranged from 312-359/μL in the 3 arms. This study included 47, 39, and 47 nRTI-experienced subjects in arms I, II, and III, respectively. At 32 weeks' follow-up, there were 32%, 20%, and 35% (ITT) and 60%, 35%, and 65% (OT) of experienced subjects with <50 copies HIV-1 RNA/mL of plasma.

Saquinavir-SGC and/or nelfinavir and/or nRTIs.– The 72-week follow-up data of the SPICE study were presented (Table 2) **(Abstract 389)**. In this trial 157 subjects (approximately 50% being nRTI experienced) were randomized to 1 of 4 arms: saquinavir-SGC 1200 mg tid/2 nRTIs (arm A); nelfinavir 750 mg tid/2 nRTIs (arm B); saquinavir-SGC 800 mg tid/nelfinavir 750 mg tid/2 nRTIs (arm C); saquinavir-SGC 800 mg tid/nelfinavir 750 mg tid (arm D). The mean baseline plasma HIV-1 RNA values and CD4+ cell counts ranged from 4.7-4.8 $\log_{10}$ copies/mL and 300-334/μL. The numbers of experienced subjects in arms A through D were 12, 12, 24, and 24, respectively. At 72 weeks, by ITT analysis and defining missing data equal to failure, the percentages of nRTI-experienced subjects with below 50 copies HIV-1 RNA/mL were 33%, 25%, 46%, and 21% in arms A, B, C, and D, respectively. Overall, the 4-drug regimen appeared to be superior to the other 3 arms in terms of suppression of plasma HIV-1 RNA levels and time to virologic failure.

nRTIs in combination with nelfinavir and/or efavirenz.– Albrecht et al presented updated 16-week data from ACTG 364, which was a randomized Phase II, roll-over trial (from ACTG 175, 302, and 303) of 195 highly nRTI-experienced subjects on stable nRTI therapy but who were protease inhibitor and NNRTI naive (Table 2) **(Abstracts 489, 138)**. The median baseline plasma HIV-1 RNA level and CD4+ cell count were 3.9 $\log_{10}$ copies/mL and 389/μL, respectively. Subjects were randomized to 1 of 3 arms containing 1 or 2 new nRTIs with either nelfinavir (arm I); or efavirenz (arm II); or nelfinavir/efavirenz (arm III). At 48 weeks of follow-up in arms I, II, and III, the proportion of subjects with <500 copies/mL HIV-1 RNA in plasma were 35%, 60%, and 74%, respectively (3-way P=0.001). Across the 3 arms the median increase in CD4+ cell counts was 94/μL at 40 to 48

weeks. Virologic failure was significantly associated with prior lamivudine experience (odds ratio [OR], 5.2), baseline HIV-1 RNA level (OR, 2.4 per log increase), and the number of reverse transcriptase mutations (OR, 1.3 per mutation). Overall, in this study a highly significant difference in virologic suppression was noted among the 3 treatment arms favoring the efavirenz/nRTI and efavirenz/nelfinavir/nRTI arms over the nelfinavir/nRTI arm.

Salvage Therapies for nRTI- and Protease Inhibitor-Experienced Subjects:

Adefovir/efavirenz/abacavir/nelfinavir in nRTI/indinavir failure. – Hammer et al (ACTG 372B) investigated a variety of salvage regimens in 94 NNRTI naive, highly nRTI-experienced subjects in whom a stable regimen of zidovudine (or stavudine)/lamivudine/indinavir failed (Table 2) **(Abstract 490)**. Median baseline HIV-1 RNA levels and CD4+ cell counts were 4.59 $\log_{10}$ copies/mL and 196/μL. Subjects were randomized to 1 of 4 arms, comprising an adefovir/efavirenz backbone in combination with (abacavir or 1 or 2 nRTIs) plus (nelfinavir or nelfinavir-placebo), see Table 2. The percentages of subjects at 16 weeks with plasma viral RNA levels <500 copies/mL in the nelfinavir versus placebo-nelfinavir arms were 45% versus 24%, respectively (P=0.046). The mean increases in CD4+ cells from baseline in the nelfinavir and nelfinavir-placebo arms were 60/μL and 14/μL. At week 16, the percentages of subjects with plasma HIV-1 viral loads <500 copies/mL in the abacavir and nRTI-containing arms were 37% and 32%, respectively (P= 0.623), and the mean increases in CD4+ cells from baseline were similar in each arm, approximately 36/μL. Although there was under accrual within this study, in this indinavir-failure population, efavirenz in combination with adefovir, nelfinavir, and nRTI therapy provided superior suppression of plasma HIV-1 RNA at 16 weeks of follow-up compared with regimens without nelfinavir.

Ritonavir/saquinavir/nRTIs in nelfinavir/nRTI failure.– Tebas et al presented the 60-week follow-up of 26 subjects in whom a nelfinavir/nRTI-based regimen failed **(Abstract 392)**. At entry subjects had a median viral load of 4.7 $\log_{10}$ copies/mL, a median CD4+ cell count of 222/μL, and a median of 55 weeks of nelfinavir experience. Subjects received stavudine/lamivudine/ritonavir/saquinavir-SGC. At week 60, 24 of 26 remained in the study, 58% (LOCF analysis) having plasma HIV RNA <500 copies/mL. Mean gains in CD4+ counts of 120/μL were maintained at 48 weeks. Baseline protease genotype was not predictive of virologic outcome at 48 weeks. However, a baseline viral load of >30,000 copies/mL was associated with a greater risk of virologic failure at the same time point (P=0.03; relative risk [RR], 2.5).

NRTI-, NNRTI-, and Protease Inhibitor-Experienced Subjects

Data were presented from CNA 2007, an ongoing open-label study evaluating salvage therapy with abacavir/efavirenz/amprenavir in 101 subjects in whom a stable protease inhibitor-based regimen failed. Prior nRTI (with the exception of abacavir), NNRTI, and protease inhibitor exposure was allowed.

Baseline genotypic analysis revealed that 71% of isolates had 5 or more reverse transcriptase-associated mutations (nRTI + NNRTI). NNRTI-associated mutations were observed in 38% of isolates and a majority of isolates had 5 or more protease-associated mutations (83% of the 65 virology substudy subjects). Baseline phenotypic analysis demonstrated that 57%, 25%, and 45% of baseline isolates were phenotypically resistant to abacavir, efavirenz, and amprenavir, respectively. The levels of phenotypic cross-resistance within the nRTI, NNRTI, and the protease inhibitor classes were also high, 19% to 90%, 25% to 40%, and 45% to 84%, respectively.

Of the first 65 subjects reaching 16 weeks, only 34% had viral load reduced to below 400 copies/mL or a (1 $\log_{10}$ decline in plasma RNA level. At 16 weeks the highest proportion of subjects with HIV-1 RNA values <400 copies/mL (53%) was observed in NNRTI-naive subjects with baseline plasma HIV-1 RNA values <4.6 $\log_{10}$ copies/mL. The presence of several specific mutations or groups of mutations was associated with a poorer virologic outcome (Table 2).

Significant predictors of failure of suppression of plasma viral load (1 $\log_{10}$ or to <400 copies/mL were: (1) higher baseline viral loads (P=0.0005) and (2) phenotypic resistance to efavirenz (P=0.006) or to abacavir (P=0.006). Suppression of viral load to <400 copies/mL was observed in 5 of 9 (56%) subjects with baseline isolates susceptible to all 3 drugs and only 4 of 21 (19%) of subjects with baseline isolates susceptible to 1 or no drugs. These data demonstrate the utility of genotypic and phenotypic assay results in predicting virologic failure (and to a lesser extent response) of salvage regimens **(Abstract 133)**.

STRATEGIES FOR THERAPY

Antiretroviral Drug Substitution in Stably Suppressed Individuals

The relative merits of substituting an NNRTI for a protease inhibitor in individuals on stable therapy was

addressed in 2 studies. Ruiz et al described a study in which 60 subjects on stable protease inhibitor-containing regimens for 9 months or longer and with plasma HIV-1 RNA levels below 400 copies/mL for 6 months were randomized to stavudine/lamivudine/protease inhibitor or to stavudine/didanosine/nevirapine **(Abstract LB14)**. Follow-up data at 3 months were available for 14 and 15 subjects in the protease inhibitor and NNRTI arms, respectively. In both groups there were no significant changes in CD4+ cell counts from baseline, and plasma HIV-RNA levels remained <50 copies/mL. There was a statistically significant decrease in triglyceride and cholesterol levels from baseline in the NNRTI arm. The switch to nevirapine, empirically covered with antihistamines, was well tolerated with no recorded rash. Although the follow-up time in these studies is relatively short, these data suggest that NNRTI substitution might be a viable alternative in protease inhibitor-intolerant patients.

These findings were echoed by those of Raffi et al in a similarly constructed study in which subjects on stable protease inhibitor-based therapy switched to nevirapine (n=16) or efavirenz (n=2) **(Abstract 381)**. After a median follow-up time of 17 weeks, 16 of 18 had plasma HIV-1 RNA levels below assay detection limits. The switch was generally well tolerated with nevirapine-associated rash developing in only 1 of 16 subjects.

Intensification

Abacavir added to zidovudine/lamivudine.– Rozenbaum et al presented the 48-week follow-up of CNA 3009, an open-label multicenter trial in 52 subjects, in which abacavir was added to the dual nRTI regimen of zidovudine/lamivudine of more than 12 weeks' duration **(Abstract 377)**. The median baseline CD4+ cell count and HIV-1 RNA level were 543/μL and 2.88 log10 copies/mL, respectively. The regimen was well tolerated for up to 48 weeks when, by on-treatment analysis, 46% of subjects had a plasma viral load <20 copies/mL (ITT analysis). The median increase in CD4+ cell count at 48 weeks was 114/μL.

Abacavir added to a stable antiretroviral background therapy.–Ait-Khald et al presented 16-week follow-up data from a randomized, double-blind, placebo-controlled trial in which abacavir or placebo was added to stable background therapy (CNA 3002) **(Abstract 114)**. In the abacavir and placebo arms, 92 and 93 subjects were enrolled, respectively. The median CD4+ cell counts and plasma HIV-1 RNA levels in the abacavir and placebo groups were 408 and 411/μL and 3.68 and 3.52 $\log_{10}$ copies/mL, respectively. The background therapy was similar in both groups, ie, dual nRTI in 81% and 78% in abacavir and placebo arms, respectively. At 16 weeks, 39% and 8% of the abacavir and placebo recipients, respectively, had plasma HIV-1 RNA levels <400 copies/mL (ITT, P<0.001). These differences remained significant for lamivudine-experienced and -naive subjects. At 16 weeks of follow-up the median CD4+ cell count was modestly increased in the abacavir arm (by 19/μL) but declined in the placebo arm (by 3/μL) (P=0.09). The presence of the 184V mutation did not appear to diminish the efficacy of abacavir-containing regimens **(Abstracts 378, 114)**.

RESISTANCE

Resistance Prevalence in Primary Infection

Wegner et al **(Abstract LB9)** presented genotypic and phenotypic analyses of 95 and 91 isolates, respectively, derived from 114 drug-naive subjects in North America who had documented seroconversion within the last 3 years. Isolates were tested against currently available NNRTIs, nRTIs, and protease inhibitors using a recombinant virus assay (Virco). Phenotypically, isolates were defined as resistant, intermediate, or susceptible (>10-, 5 to 10-, and <5-fold relative decreases in susceptibility, respectively). Overall, 6% of isolates expressed high-level phenotypic and genotypic resistance to 1 drug class. Intermediate levels of phenotypic and genotypic resistance were observed in 21% and 17% of isolates. Resistance to NNRTIs accounted for most of the observed resistance. Genotypic evidence of resistance to nRTIs, NNRTIs, and protease inhibitors was observed in 4%, 15%, and 10% of isolates, respectively; phenotypic resistance was observed in 7%, 27%, and 1% of isolates, respectively.

One multidrug-resistant isolate was observed demonstrating mutations at codons 10, 73, 77, and 90 in the protease and codons 67, 70, 100, and 184 in the reverse transcriptase. This isolate demonstrated high-level phenotypic resistance to nelfinavir (intermediate-level resistance to the other protease inhibitors) and high-level resistance to lamivudine (intermediate-level resistance to zidovudine, nevirapine, and efavirenz).

A similar study by Little et al **(Abstract LB10)** evaluated phenotypic susceptibilities in isolates derived from 69 subjects in North America who were less than 12 months from documented seroconversion and who had 7 or less days of prior antiretroviral therapy. The drug susceptibility assay employed was the recombinant virus assay ViroLogic, Inc with relative fold differences in susceptibilities of <2.5, 2.5-10, and >10 being used to define susceptible, intermediate, or resistant. High-level resistance was

observed in 3%, 1%, and 3% of isolates to nRTIs, NNRTIs, and protease inhibitors. Overall, 3% of isolates were resistant to 2 or more drug classes and 1% were resistant to 3 drug classes. These studies suggest that in the recent past within the United States, the prevalence of high-level multidrug resistance appears to be relatively low. However, the prevalence of viral resistance overall appears to be increasing and is a worrisome trend.

The Clinical Utility of Resistance Testing

The impact on response to therapy of a mutation at codon 215 of reverse transcriptase.– Mayers et al (ACTG 244/RV79) evaluated the response in zidovudine-treated subjects of a switch to zidovudine/didanosine or zidovudine/didanosine/nevirapine at the time of developing the 215Y or F mutations and compared this response with similarly treated controls in whom virus remained wild-type at this codon. After detection of the 215 mutation there was a median CD4+ cell decline of 49 and 35/μL/year in the zidovudine/didanosine and zidovudine/didanosine/nevirapine arms, respectively, in the group with the mutation mutant. This compares with the control group in which the change in therapy was associated with a median increase of 22 and 72 CD4+ cells/μL/year in the zidovudine/didanosine and zidovudine/didanosine/nevirapine arms, respectively, in follow-up. Although these data derive from a period when mono- and dual-nRTI therapies were standard, they highlight the role of the T215 Y/F mutation as a determinant of disease progression, which may be independent of resistance phenotype.

Mutations in the reverse transcriptase and protease genes as predictors of failure in protease inhibitor- and nRTI-experienced subjects.– Lorenzi et al evaluated mutations in the HIV-1 reverse transcriptase and protease as predictors of subsequent response to nelfinavir-based salvage therapies in 62 highly nRTI- and protease inhibitor-experienced subjects with a median baseline CD4+ cell count and plasma HIV-1 RNA viral load of 133/μL and 5.16 $\log_{10}$ copies/mL, respectively. Subjects had significant prior protease inhibitor and nRTI exposures, but few (<5%) had prior NNRTI exposure. Baseline mutations to nRTIs included zidovudine-associated mutations (80%), 184V (75%), 69D (11%); and to protease 46I/L (21%), 82A/T (45%), and 90M (39%). The D30N mutation associated with nelfinavir exposure was not recorded in any isolate at baseline. Salvage regimens comprised nelfinavir in combination with saquinavir/1 to 2 nRTIs (40%), or with NNRTI/nRTI (23%), or with 2 to 4 nRTIs (37%). At 4 to 12 weeks' follow-up, the median (range) decrease in plasma HIV-1 RNA levels was -0.38 (-3.17 to +1.09). Importantly, only 3% of subjects recorded plasma HIV-1 viral loads of <400 copies/mL. In multivariate analysis the baseline total number of mutations in the reverse transcriptase and protease was the only factor independently predictive of virologic response (univariate RR, 0.14 $\log_{10}$ per mutation; $P<0.0001$). The CD4+ cell count, baseline plasma HIV-1 RNA level, and CDC stage were not predictive of outcome **(Abstract 140)**. These data complement those of Race et al, who observed that the risk of phenotypic protease inhibitor cross-resistance in vitro increases as the number of protease mutations increases **(Abstract 119)**.

Phenotypic assays: drug susceptibilities as predictors of response to salvage regimens employing 6 or more antiretrovirals.– Among individuals failing current standard regimens and who have broad cross-class experience, the possibility of utilizing multiple agents in so-called mega-HAART regimens is being widely investigated. Miller et al evaluated baseline plasma HIV-1 drug susceptibilities, as determined by the Virco recombinant virus assay, in relation to response to treatment with 6 or more antiretrovirals in 24 highly antiretroviral-experienced subjects **(Abstract 130)**. The protease inhibitor regimens used included ritonavir/(nelfinavir or saquinavir) versus nelfinavir/indinavir. The NNRTIs used included efavirenz, nevirapine, or delavirdine. Baseline drug susceptibilities revealed resistance to zidovudine, abacavir, and NNRTIs in 15 (63%), 11 (46%), and 10 (42%) subjects, respectively. Resistance to 3 or more protease inhibitors was observed in 13 (54%) subjects, 6 of whom exhibited high-level cross-resistance. Subjects were followed up for a median of 8 months when an increase in CD4+ cell count >100/μL was recorded in 19 of 24 subjects. Defining a response as a sustained plasma HIV-1 viral load <500 copies/mL, the numbers of responders, nonsustained responders, and failures were 10 (50%), 8 (33%), and 6 (24%), respectively. Seven of 10 responders, and 0 of 6 failures were treated with a minimum of 4 "active" drugs. Thus for subjects treated with mega-HAART regimens, the inclusion of multiple agents to which HIV-1 isolates are susceptible will more likely be successful. These data suggest a role for phenotypic testing in optimizing such complex regimens and raise the possibility of simplifying such regimens by deleting drugs to which resistance is documented.

Multinucleoside Resistance

Data continue to emerge relating to groups of mutations in the HIV-1

reverse transcriptase associated with multi-nRTI resistance. The following mutations, when occurring in a background of zidovudine resistance mutations (+/- the M184V mutation), are associated with moderate to high levels of cross-resistance to all currently available nucleoside analogs: single, double, or triple codon insertions at codons 68-69 (including S/SS/SA/SE/SAG), T69D/N/S/A, and the V75M mutation **(Abstracts 122, 123, 133, 135, S34)**.

RT codon 68 and 69 insertions. Lukashov and Ross described 7 isolates demonstrating 2 codon insertions between reverse transcriptase codons 68 and 69 **(Abstracts 122, 123)**. The treatment histories in these subjects varied, but most had previously received lamivudine and 5 of 7 had received zidovudine. Notably 2 of 7 subjects had only received stavudine and lamivudine in combination. In the isolates from these latter 2 subjects the 2 codon insertion (S-A) was observed in the absence of the typical zidovudine-associated resistance mutations.

The Q151M resistance complex.– The complete Q151M reverse transcriptase resistance complex (A62V, V75I, F77L, F116Y, and Q151M) is associated with a relatively high level of resistance to all currently available nRTIs. The occurrence of this complex in whole or part is typically observed in viral isolates that do not display mutations associated with resistance to other nRTIs. Two uncommon viral isolates were described in which the Q151M mutation was observed to emerge in association with multiple zidovudine mutations or where the complete Q151M complex was observed in association with the M184V mutation **(Abstract 121)**. Recombinant virus susceptibility assays demonstrated that the complete Q151M complex + M184V demonstrated greater resistance than the Q151M + zidovudine resistant complex.

Two studies described the diminished in vitro susceptibilities of recombinant HIV-1 isolates bearing the Q151M multi-nRTI resistance mutation **(Abstracts 113, 124)**. Notably, none of the 5 recombinant viruses examined by Van et al was susceptible to abacavir, with 3 of 5 isolates displaying high-level abacavir resistance. However, Anton et al described that isolates bearing the Q151M mutation exhibited only minor (2.5-fold) decreases in susceptibility to both adefovir and PMPA **(Abstract 124)**.

Impact of multidrug resistance in clinical trials.– Poorer response to salvage therapy with abacavir, efavirenz, and amprenavir was observed with each of the following baseline reverse transcriptase mutations or mutation complexes, (3 zidovudine-associated mutations (+/- 184V mutation), the T69D mutation, the 68-69 insertion variants, and the Q151M complex **(Abstract 133)**. Montoya et al described early failure in 2 of 6 subjects on a salvage regimen of adefovir, efavirenz, didanosine, and hydroxyurea in association with the presence at baseline of reverse transcriptase mutations 41L, 69D/S/A, and 215Y in combination **(Abstract 135)**.

Cross-Resistance

Protease inhibitor cross-resistance.– Race et al evaluated in vitro resistance to indinavir, saquinavir, ritonavir, nelfinavir, and amprenavir of HIV-1 isolates derived from 108 plasma samples from subjects failing protease-containing regimens, principally indinavir, ritonavir, and saquinavir. The drug susceptibility assay used was a novel single-cycle recombinant virus assay (scRVA). The incidence of cross-resistance among the currently available protease inhibitors was high, 60% to 90%. However, the level of cross-resistance to amprenavir was somewhat lower (37% to 40%). Resistance to indinavir was strongly associated with resistance to both ritonavir and nelfinavir. Over 80% of isolates with the mutations V54 + A82 + (I10 or V/Y71) were resistant to 4 or 5 protease inhibitors. Overall, a correlation was noted between the number of protease mutations observed and the number of protease inhibitors to which an isolate was resistant **(Abstract 119)**.

Genotypes and phenotypes of efavirenz resistance and cross- resistance.– Bachelor et al, employing data derived from 3 clinical trials, described rebound in plasma HIV-1 viral load in subjects on efavirenz-based regimens in association with the emergence of the sentinel K103N RT mutation alone or more frequently when paired with the L100I, V108I, or P225H mutations **(Abstract 109)**. The resistance profiles to currently available NNRTIs of recombinant viruses carrying the above mutations were examined **(Abstract 110)**. Recombinant viruses carrying the K103N mutation alone displayed 19-, 40-, and 24-fold reductions in susceptibilities to efavirenz, nevirapine, and delavirdine, respectively. The level of NNRTI cross-resistance was further increased in mutants carrying the K103N mutation in combination with the L100I, V108I, or P225H mutations. Thus recombinant viruses bearing the K103N mutation in isolation or paired with L100I, V108I, or P225H mutations were cross-resistant in vitro to all currently available NNRTIs. The combination L100I/ K103N carried the highest level of cross-resistance to currently available NNRTIs.

Virologic Failure of Indinavir-Based Therapies with "Wild- Type" Rebound of HIV-1 RNA in Plasma

Several studies dealt with the observation of "wild-type" protease sequences in subjects with rebound of plasma HIV-1 RNA levels on indinavir-containing regimens. ACTG 343 previously demonstrated the high failure rate of induction/maintenance strategies in zidovudine-experienced subjects. Havlir et al presented updated data from ACTG 343, describing 9 and 17 subjects with virologic rebound who received indinavir and zidovudine/lamivudine/indinavir, respectively, and comparing these with 10 controls in whom virologic suspension was maintained **(Abstract LB12)**. These 26 isolates were susceptible to indinavir using the ViroLogic phenotype assay. The only protease inhibitor-associated mutation observed was the M46L change in 1 of 26 subjects. Among isolates exposed to lamivudine, 14 of 17 (82%) possessed the 184V mutation and were resistant. Although mean random indinavir levels in the rebound and control groups were comparable, the percent of subjects with at least one indinavir level below detection was higher in the triple-drug failure group.

Similar findings were described by Descamps et al who presented an analysis of the Trilege study in which a comparable induction/maintenance strategy was evaluated in antiretroviral-naive subjects **(Abstract 493)**. Among 29 subjects taking indinavir/zidovudine or indinavir/zidovudine/lamivudine who experienced on-treatment rebound in plasma HIV-1 RNA, "wild-type" protease sequence was observed in 28 (97%). More detailed pharmacokinetic profiles in these subjects revealed at least one indinavir level below detection limits (0.5 ng/mL) in 13 of 26 subjects, while 4 of 26 had subtherapeutic indinavir levels.

These observations were consistent with those of Holder et al who found no indinavir-associated resistance mutations in 69% to 78% of isolates derived from indinavir-treated subjects experiencing an on-treatment rebound in plasma viral RNA, while reverse transcriptase mutations were observed in more than 70% of such isolates (492). Importantly, it does not appear that this phenomenon is restricted to indinavir as wild-type protease rebound in plasma has been observed in 90% of protease inhibitor-naive subjects in whom amprenavir/zidovudine/lamivudine therapy is failing **(Abstract 118)**.

Activity of Adefovir Dipivoxil Against Zidovudine and Zidovudine/Lamivudine-Resistant Isolates

Adefovir dipivoxil (bis-POM PMEA) is the oral prodrug of adefovir, a nucleotide reverse transcriptase inhibitor (nRTI) with in vitro potency equivalent to current nRTIs. While isolates possessing zidovudine resistance mutations show diminished susceptibility to adefovir, this resistance may be reduced significantly by the incorporation of the M184V reverse transcriptase mutation, associated with lamivudine resistance. Notably, the presence of the M184V mutation in isolation renders HIV-1 isolates approximately 2-fold more susceptible to adefovir than wild-type virus **(Abstracts 124, 137)**.

These in vitro data were supported by the 48-week results of GS-96-408, in which the relative benefits of adding adefovir (n=219) or placebo (n=223) to stable background therapy were evaluated. At 24 weeks' follow-up, plasma HIV-1 RNA levels remained unchanged in the placebo group, while the addition of adefovir produced a modest (0.4 $\log_{10}$ copies/mL) decrease in plasma HIV-1 RNA levels that was sustained for 32 to 48 weeks. However, the virology substudy of 31 patients showed that among subjects remaining on stable background therapy, the degree of suppression of plasma HIV-1 RNA levels differed according to baseline reverse transcriptase genotype, M184V (-0.54 $\log_{10}$) > wild-type >M184V + $\geq$ 1 zidovudine mutation >$\geq$ 1 zidovudine mutation (+0.16 $\log_{10}$ copies/mL). Interestingly, zidovudine-associated mutations emerged after 24 weeks on adefovir-containing regimens among subjects treated also with zidovudine or stavudine **(Abstracts 124, 137)**.

Abacavir Efficacy in Relation to Baseline Reverse Transcriptase Genotypic Profiles

Lanier et al evaluated virologic outcomes at 12 to 24 weeks in nRTI-experienced subjects who received abacavir-based therapies **(Abstract 134)**. This study evaluated 88 subjects previously enrolled variously in CNA 2003, 3001, 3002, and 3009 studies in which abacavir was added to stable background therapy (comprising nRTIs, NNRTIs, or protease inhibitors). Median CD4+ cell counts and plasma HIV-1 RNA levels ranged from 146 to 492/μL and 3.52 to 4.83 $\log_{10}$ copies/mL, respectively. At 12 to 24 weeks' follow-up the percentage of subjects achieving plasma HIV-1 RNA levels below 400 copies/mL with baseline reverse transcriptase genotypes was 54% (wild-type), 68% (M184V alone), 55% (1 or 2 mutations), and 8% (3 or more mutations), respectively. Thus, although the presence of the M184V mutation in isolation at baseline conferred a modest 2-fold decrease in susceptibility to abacavir relative to wild-type, this alone did not appear to affect the proportion of subjects in whom plasma HIV-1 RNA levels were <400 copies/mL in follow-up. However, the presence of 3 or more reverse transcriptase mutations at baseline, a history of receiving 3 or more antiretrovirals, and a history of receiving

antiretrovirals for more than 18 months were each associated with a poorer response to abacavir (P= 0.001).

Utility of Resistance Testing in Clinical Management

The impact of HIV-1 genotyping on clinical decision making and virologic outcomes was evaluated in the Genotypic Antiretroviral Resistance Testing (GART) study **(Abstract LB8)**. In this study 153 subjects with a greater than 3-fold increase in plasma HIV-1 RNA after 16 weeks on standard protease inhibitor-based therapies were enrolled. There were 2 study arms. In the GART arm, the patient's physician could choose to follow the recommendations of an individualized GART report. This report was prepared by individuals familiar with interpretation of HIV-1 genotypic data and also considered the subjects antiretroviral histories, CD4+ cell counts, and plasma HIV-1 RNA levels. In the no-GART arm, the patient's physician made treatment decisions without the GART report. The primary endpoint was the change in HIV-1 viral load as an average of the 4- and 8-week changes from baseline.

At entry, 78 and 75 subjects were enrolled in the GART and no-GART arms, respectively. The mean entry CD4+ cell counts and median plasma HIV-1 RNA levels were 230/μL and 4.6 $\log_{10}$ copies/mL, respectively. At entry, most subjects were receiving lamivudine plus (stavudine or zidovudine) plus (indinavir or nelfinavir). In the GART and no-GART arms, the first protease inhibitor-based regimen was failing in 53% and 44% of subjects, respectively. Baseline genotypic data revealed that 73% of isolates had 1 major mutation in both reverse transcriptase and protease genes, 20% had 1 major mutation in the reverse transcriptase gene alone, and 5% had no major mutations in either gene. The major reverse transcriptase mutations were M184V (82%) and 215Y/F (61%). The major protease mutations included D30N (14%), V82A/I/D (34%), and L90M (31%). The plasma HIV-1 RNA responses in the GART and no-GART arms were -1.17 $\log_{10}$ and -0.51 $\log_{10}$ copies/mL from baseline (P=0.001). This difference between the 2 arms remained significant when controlling for subject demographic group, the number of baseline antiretrovirals, the CD4+ cell count and plasma HIV-1 RNA level at baseline, and the study week of follow-up.

The change in plasma viral RNA from baseline was related to the number of active drugs prescribed in each arm, ranging from +0.14 to -1.25 $\log_{10}$ copies/mL for the use of ≤ 1 to ≥ 4 active drugs, respectively. Three or more active drugs were used in 86% and (50% of GART and no-GART arms, respectively. However, within the GART arm, in only 54% of cases did the physician actually prescribe the recommended GART regimen. When the data were analyzed by GART adherence, the effect of GART report is more obvious with >80% and <1% adherence associated with -1.47 $\log_{10}$ and 0.0 $\log_{10}$ copies/mL changes in plasma HIV-1 RNA from baseline, respectively (P=0.006). These data highlight the utility of appropriately applied genotypic interpretations as an adjunct to standard care in individuals failing current standard therapies.

Virologic Response in Specific Body Compartments

Seminal Plasma

Depasquale et al examined the protease sequences in blood and seminal plasma in 10 antiretroviral-naive subjects treated with amprenavir-based therapy who had detectable viral load in seminal plasma at baseline **(Abstract LB11)**. A rebound of viral load in seminal and blood plasma in 2 patients was associated with amprenavir-associated mutations L10I and I50V in both blood and seminal plasma virus. In 2 patients HIV RNA rebound in blood and seminal plasma was associated with amprenavir mutations only in virus in blood plasma. In 1 subject the L90M mutation was observed transiently in seminal plasma only.

Cerebrospinal Fluid

Stavudine/lamivudine/nelfinavir, viral load response, and stavudine levels.– Haas et al evaluated the impact of stavudine/lamivudine/nelfinavir on cerebrospinal fluid (CSF) and plasma viral load in 3 HIV seropositive, antiretroviral-naive subjects, using highly intensive sampling of CSF and plasma at baseline and after 4 to 7 days of therapy **(Abstract 405)**. For these 3 subjects the "day 0" plasma HIV-1 RNA levels ranged from 4.69 to 4.87 $\log_{10}$ copies/mL and the mean CSF RNA levels were 3%, 45%, and 93% of plasma levels, respectively. In follow-up, day 4 to 7, the plasma HIV-1 RNA levels fell by 1.33, 0.81, 1.11 $\log_{10}$ copies/mL, and CSF levels fell by 0.81, 1.18, and 0.037, respectively. The CSF:plasma ratios of declines were 0.61, 1.48, and 0.32. CSF levels of stavudine varied among subjects but were approximately 39% of plasma levels. These data suggest, at least in the short term, that variable rates of HIV-1 RNA decay may occur in CSF in individuals taking potent antiretroviral therapies.

Indinavir levels in CSF and serum and relation to viral load.– Letendre et al compared CSF and serum indinavir levels with plasma HIV-1 RNA levels in 22 HIV seropositive subjects on stable therapy with indinavir plus 2

nRTIs. Subjects had a median CD4+ cell count of 243/μL and median plasma and CSF RNA levels of 3.1 and 2.3 $\log_{10}$ copies/mL, respectively **(Abstract 407)**. Samples were drawn at differing times along the dose interval. Serum indinavir and plasma HIV-1 RNA levels were inversely correlated (P=0.03). No correlation was evident between CSF indinavir and HIV-1 RNA levels; however, 18 of 22 CSF samples had <200 copies/mL. CSF indinavir levels demonstrated less variation than serum indinavir levels and were approximately 6% (5% to 9%) of serum levels. This study demonstrated appreciable penetration of indinavir into the CSF.

Ritonavir/saquinavir, viral load response, and protease inhibitor levels.– In the Prometheus study, Gisolf et al evaluated differing viral load responses in CSF and plasma in 27 HIV-1 seropositive subjects who received twice daily regimens of ritonavir/saquinavir (400/400 mg), with or without stavudine **(Abstract 403)**. At week 12 in the ritonavir/saquinavir and ritonavir/saquinavir/stavudine groups, 4 of 14 (29%) and 12 of 13 (92%) subjects, respectively, had CSF viral loads below quantification (P=0.001). In 21 of 25 subjects, CSF protease inhibitor levels were below detectable limits. These data suggest that the CSF penetration of ritonavir and saquinavir when used in combination may be suboptimal.

Adjunctive Agents

Interleukin-2 Therapy

Clinical trials employing interleukin-2 (IL-2) in conjunction with anti- retroviral therapy in order to enhance immune recovery and as a possible means of purging latent HIV-1 from the resting CD4+ T-cell reservoir were presented. In 4 studies presented at the Conference, the combination of antiretroviral therapy with IL-2 resulted in substantial CD4+ cell count increases and no significant viral rebounds relative to antiretroviral therapy alone **(Abstracts 354, 355, 356, 357)**. For example, Losso et al related data from a randomized, dose-ranging open-label trial employing antiretroviral therapy with and without subcutaneous IL-2 in 73 patients with baseline CD4+ cell counts above 350/μL (mean, 506/μL) and a mean plasma HIV-1 RNA level of 2.96 $\log_{10}$ **(Abstract 354)**. At week 24, CD4+ cell count increases were significantly greater (200/μL versus <50/μL) with the IL-2-containing regimen than with antiretroviral therapy alone (P<0.001). At the same time, the percentages of patients with plasma HIV-1 RNA below 500 copies/mL were equivalent (70% versus 62%, respectively, P=0.46). The most common adverse effects were fever, malaise, and rash.

To examine the potential of concurrently administered IL-2 and antiretroviral therapy in eliminating latent HIV-1 reservoirs, Prins et al related data collected from a study combining IL-2 and OKT-3 with antiretroviral therapy with the intent to test the above hypothesis **(Abstract LB6)**. Three patients with long-term antiretroviral suppression of plasma HIV-1 RNA levels (a range of 9 to 15 months of therapy resulting in <5 copies/mL for 34 to 37 weeks) were enrolled and treated with OKT-3 and IL-2. While HIV-1 replication was transiently stimulated in these patients as reflected by plasma HIV-1 RNA levels increasing above measurable levels, the number of resting lymphocytes harboring HIV-1 DNA remained <1 per 10^6 cells in 2 of the patients. Unfortunately, significant lymphopenia and other adverse effects resulted from the treatment.

Hydroxyurea-Containing Therapies

Primary infection.– Zala et al evaluated the impact of stavudine/didanosine/nevirapine with and without hydroxyurea in 22 subjects treated within 6 months of HIV-1 infection **(Abstract 399)**. At 24 and 36 weeks the numbers of subjects with plasma HIV-1 RNA levels <50 copies/mL in '+' hydroxyurea and '-' hydroxyurea arms were 8 of 10 and 7 of 8, and 5 of 6 and 4 of 5, respectively. The relative increases in CD4+ cell counts at 36 weeks in the '+' hydroxyurea and '-' hydroxyurea arms were + 175 and + 415/μL. Notably 1 subject, treated approximately 1 month after a confirmed diagnosis of primary infection with stavudine/didanosine/nevirapine without hydroxyurea and who had suppression of plasma HIV-1 RNA levels to below 50 copies/mL on treatment at 8 weeks, stopped his therapy after 20 weeks. To date, 18 weeks after stopping therapy, this subject still had plasma HIV-1 RNA levels below the limit of detection.

Treatment of established disease with hydroxyurea/didanosine.– In a complex study, Frank et al evaluated the relative merits of didanosine monotherapy versus various combination regimens of hydroxyurea with didanosine, including the delayed or immediate addition of hydroxyurea to didanosine therapy **(Abstract 402)**. Seventy-two subjects with a median CD4+ cell count of 370/μL and a median $\log_{10}$ plasma HIV-1 RNA level of 4.42 were enrolled. All were didanosine-naive, and 45% were antiretroviral-naive. This study noted no effect of 4 weeks of hydroxyurea monotherapy on plasma viral load, and a greater reduction in plasma viral load at 8 weeks in the hydroxyurea/didanosine arm than in the didanosine monotherapy arm, 1.57

and 0.83 $\log_{10}$, respectively (P=0.01). No significant change was observed in plasma viral load 12 weeks after hydroxyurea was added to didanosine monotherapy.

IMMUNE RECONSTITUTION

Several presentations elucidated a more detailed picture of the immunologic ramifications of potent antiretroviral therapy. The major themes in this area were outlined in a symposium by Autran **(Abstract S44)**. These include (1) the long-term characteristics of naive CD4+ cell regeneration and (2) the restoration of recall antigen and HIV-1 specific responsiveness.

Potent Antiretroviral Therapy and Naive CD4+ T-cell Regeneration

As demonstrated by Autran et al long-term naive CD4+ T-cell regeneration is dependent on viral suppression rather than the degree of HIV-1 disease at baseline **(Abstract S44)**. After 2 years of potent antiretroviral therapy, no plateau in the increase of naive CD4+ cells has yet been observed. Moreover, it was estimated that in order to attain normal levels of naive cells, the duration of HIV-1 suppression would be approximately 12 months if basal CD4+ cell counts were above 400/μL or 6 to 8 years if basal CD4+ cell counts were below 100/μL. In addition to long-term HIV-1 suppression, naive CD4+ cell regeneration is also dependent on retained thymic function, this based on a lack of naive cell recovery in patients with Hodgkin's disease who underwent thymic irradiation.

Potent Antiretroviral Therapy and Response to Recall Antigens

The observation that the early initiation of potent antiretroviral therapy prevents loss of responsiveness to mitogens and recall antigens was made by several groups **(Abstracts 322, 324, S44)**. For example, a presentation by Carvelain et al demonstrated that the T-cell response to cytomegalovirus (CMV) 2 years after initiation of highly active antiretroviral therapy (HAART) in patients with advanced disease (mean CD4+ cell count of 369/μL) was 64% versus 100% in patients with early (mean CD4+ cell count of 851/μL) HIV-1 disease **(Abstract 324)**. Similarly, in a study by Schrier et al the responsiveness to CMV in patients with advanced disease (CD4+ cell count <100/μL) increased from 15% before active antiretroviral therapy to approximately 70% after initiation of therapy **(Abstract 325)**. As with other studies, the immune recovery was related to the amplitude of CD4+ cell response rather than the plasma HIV-1 RNA level **(Abstracts 325, 326)**.

The clinical correlation of the above-mentioned increases of in vitro CMV specific immune reactivity after active antiretroviral therapy was demonstrated by Jouan et al in a study that enrolled 47 HAART-treated patients with prior CMV retinitis **(Abstracts S44)**. Of these subjects, only 2 had CMV relapses in 20 months. No specific CMV reactivity was demonstrable in these 2 individuals. Antigen-specific immune restoration, therefore, appears to be functional and may allow for the subsequent withdrawal of prophylactic antimicrobial regimens.

HIV-1 Specific Immune Response

The initiation of potent antiretroviral therapy early in acute HIV-1 infection results in a significant increase in HIV-1 specific immune responses **(Abstracts 23, 324, S44)**. Autran et al presented a study of 52 patients treated with HAART for 2 to 3 years after being initiated in primary, intermediate (CD4+ cell count 250-400/μL), and advanced (CD4+ cells <250/μL) HIV-1 disease **(Abstract S44)**. Recovery of HIV p24 antigen response was only observed in subjects in whom therapy was initiated in primary infection (approximately 50% recovered p24 antigen reactivity), but not in the latter 2 groups **(Abstracts 324, S44)**. In a study of 11 acutely infected patients presented by Malhotra et al, the initiation of indinavir/zidovudine/lamivudine resulted in a significant 6-fold enhanced p24 antigen lymphoproliferative response relative to untreated controls **(Abstract 23)**.

Although an absence of restored HIV-1 and other antigen specific immune responses was observed in patients with established disease, Autran et al were able to demonstrate that in some cases, this deficit could be reversed in vitro by interleukin-12. **(Abstracts 324, S44)**.

CONCLUSION

The Conference has once again provided the field with a full description of the current state-of-the-art of antiretroviral chemotherapy and has highlighted the future directions of drug development and clinical research. It is hoped that the blueprint provided for the development of new agents, combinations and strategies to maximize antiviral potency, simplify regimens, and minimize toxicities will contribute to sustaining and furthering the progress in reducing morbidity and mortality from HIV disease witnessed in recent years. ■

Drs Coakley and Inouye are Instructors at Harvard Medical School, Division of Infectious Diseases, and are with the Beth Israel-Deaconess Medical Center

Dr Hammer is Chief, Division of Infectious Diseases at Columbia Presbyterian Medical Center, and is faculty at Columbia University College of Physicians and Surgeons

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C KATLAMA*, R MURPHY, V JOHNSON, K SQUIRES, A HORBAN, J GATELL, B CLOTET, S STASZEWSKI, R VANLEEUWEN, N CLUMECK, M MORONI, A PAVIA, SCHMIDT, J GONZALEZ-LAHOZ, F ANTUNES, R GULICK, D BANHEGYI, J MONTANER, V CALVEZ, J-P SOMMADOSSI AND J LANGE, FRANCE, U.S.A., POLAND, SPAIN, GERMANY, BELGIUM, ITALY, PORTUGAL, HUNGARY, CANADA AND THE NETHERLANDS.

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J.D.K. Wilson, G.S. Ogg, A. Kelleher, R.L. Allen, C. Davis, S. Shaunak, J. Downie, W. Dyer, C. Workman, J. Sullivan, A.J. McMichael, S.L. Rowland-Jones Dept. of Immunology and Infectious Diseases, ICSM, London, United Kingdom Molecular Immunology Group, Inst. of Molecular Med., John Radcliffe Hosp., Headington, Oxford, United Kingdom NSW Blood Bank, Sydney, Australia

26 In Vivo Migration and Antiviral Activity of Transferred HIV-1-Specific Cytotoxic T Cells.
S. BRODIE, D. LEWINSOHN, B. PATTERSON, A. RYNCARZ, L. COREY, P. GREENBERG, S. RIDDELL. U. Washington, Seattle, WA, Northwestern U., Chicago, IL, Fred Hutchinson Cancer Res. Ctr., Seattle, WA.

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C. PITCHER, C. QUITTNER, D. PETERSON, M. CONNORS, R. KOUP, V. MAINO, and L. PICKER*. Univ. of Texas Southwestern Med. Ctr., Dallas, TX; NIAID, NIH, Bethesda, MD, and Becton Dickinson Immunocytometry Systems, San Jose, CA.

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J.Binley1*, D.Schiller1, A.Hurley, G.KrAusslich, I.Jones, K.Roux, D.Ho, M.Markowitz, and J.Moore. Aaron Diamond AIDS Research Center, New York, NY;Heinrich-Pette-Institut, Hamburg, Germany; NERC,Institute of Virology, Oxford, UK; Florida State University, Tallahassee, FL.

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DF NIXON*, WM KAKIMOTO, SM DONAHOE, A GETTIE, DD HO, P MARX and R CONNOR. The Aaron Diamond AIDS Res. Ctr., New York, NY.

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R. JOHN, R. CASTILLO, S. ARANGO-JARAMILLO, B. TURNER, S. IYENGAR, AND D. SCHWARTZ*. Dept. of Molecular Microbiology and Immunology, The Johns Hopkins School of Hygiene and Public Health, Baltimore, MD 21205.

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R. IGNATIUS, K. MAHNKE, W.I. COX, H. CLEVEN, D. SCHAER, F. ISDELL, R.M. STEINMAN, & M. POPE. The Rockefeller Univ., New York, NY, Virogenetics Corp., Troy, NY

56 Genetic Manipulation of Primary Human Lymphocytes Using an HIV-1 Derived Vector System: Requirements For Transduction of Resting T Cells.
D. UNUTMAZ*, S. MARMON, R. SUTTON, V. N. KEWALRAMANI, and D. R. LITTMAN. Skirball Inst. of Biomolecular Med., New York, NY and Baylor Coll. of Med., Houston, TX.

60 SIVmac239 nef is Sufficient for Induction of Disease in Transgenic Mice.
J. SALKOWITZ AND H. KESTLER, Case Western Reserve Univ., Cleveland, OH.

109 Genotypic Correlates of In Vivo Resistance to Efavirenz
L. T. BACHELER*. B. ANTON, D. BAKER, M. BECKER, A. LASUT, M. AUJAY, L. BOLLING, K. KRAKOWSKI, J. BUNVILLE, V. WANG AND K. ABREMSKI.

110 In Vitro NNRTI Resistance of Recombinant HIV Carrying Mutations Observed in Efavirenz Treatment Failures
S. JEFFREY*, J. CORBETT and L. BACHELER. DuPont Pharmaceutical Company, Wilmington, DE.

113 The Multiple Nucleoside Analogue Resistance Mutations Confer Cross-Resistance to Abacavir.
K. VAN LAETHEM*, M. WITVROUW, J-C SCHMIT, S. SPRECHER, P. HERMANS, M. LEAL, T. HARRER, B. CLOTET, L. RUIZ, E. DE CLERCQ, J. DESMYTER, and A-M VANDAMME. Rega Inst., Belgium, CRP-Sante, Luxembourg, Inst. Pasteur and Ctr. Univ. Hosp. St. Pierre, Belgium, Virgen del Rocio Univ. Hosp., Spain, Univ. of Erlangen-Nurnberg, Germany, and Germans Trias i Pujol Univ. Hosp., Spain.

114 Genotype and Phenotype of HIV-1 in ART Experienced Adults Prior and Following Therapy with Ziagen (Abacavir, ABC) added to Stable Background Therapy (ABC+SBG)
M AIT-KHALED, C STONE, D MESOGITI, S PURDON, P VERNAZZA for the CNA3002 International Study Group. Glaxo Wellcome, Kantonsspital, St Gallen, Switzerland.

116 Mutations in the Reverse Transcriptase Genome of HIV-1 Isolates Derived from Subjects Treated with Didanosine and Stavudine in Combination.
E. COAKLEY*, J. GILLIS, and S. HAMMER. Beth Israel Deaconess Med. Ctr. and Harvard Med. Sch., Boston MA.

118 HIV Drug Resistance Analysis during Clinical Studies with the Protease Inhibitor Amprenavir.
TISDALE, M.*, MYERS, R.E., AI T-KHALED, M., AND SNOWDEN, W., Clinical Virology, Glaxo Wellcome, Stevenage, UK and the Amprenavir International Study Team.

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E. RACE*, E. DAM, V. OBRY, S. PAULOUS, and F. CLAVEL. Hop. Bichat-Claude Bernard, Paris, France.

121 Multidrug-Resistance Mutations to Dideoxynucleoside (ddN) Analogues Can Occur in Patients With Classical AZT Resistance Mutations.
A YVON, M-A VALANTIN, M MOUROUX, P BOSSI, A COUTELLIER, M BONMARCHAND, C DELAUGERRE, H AGUT, J-M HURAUX, C KATLAMA and V CALVEZ Dpts of Virology, Infectious Diseases, and Internal Medicine, Pitie-Salpetriere Hospital, Paris, France.

122 Evolutionary and Phenotypic Analysis of Multidrug-resistant HIV-1 Strains with Combinations of Insertions between Codons 68 and 69 and Amino Acid Changes in Reverse Transcriptase
V.V. LUKASHOV*, J.J. DE JONG, R. HUISMANS, M.F. JEBBINK, S.A. DANNER, S. JURRIAANS, F. DE WOLF, and J. GOUDSMIT Academic Medical Ctr., Univ. of Amsterdam, Amsterdam, The Netherlands

123 The RT 69(S) Insertion Is Observed in NRTI Experienced HIV-1 Positive Subjects with Diverse Treatment Histories.
L. ROSS*, M. JOHNSON, N. GRAHAM, M. SHAEFER and M. ST. CLAIR, Glaxo Wellcome, RTP, NC

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. E. ANTON* and M. D. MILLER. Gilead Sci., Foster City, CA.

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MAYERS D, MERIGAN T, GILBERT P for the ACTG244/RV79 Study Team. Henry Ford Hosp., Detroit, MI; Stanford Univ., Stanford, CA; Harvard Sch. of Public Health, Boston, MA; for the AIDS Clinical Trials Group and the Military Medical Consortium for Applied Retroviral Research.

130 Baseline Resistance and Virological Response to Mega-HAART Salvage Therapies
V. MILLER, P. GUTE, A. CARLEBACH, G. NISIUS, T. LEDER, C ROTTMANN, M. STURMER, K. HERTOGS, B.A. LARDER, S. STASZEWSKI. J.W. Goethe-Univ., Frankfurt, Germany; VIRCO, Mechelen, Belgium; VIRCO, Cambridge, UK.

133 HIV-1 Baseline Genotype/Phenotype and Virological Response Following Salvage Therapy with Ziagen (Abacavir, ABC), Amprenavir (APV), and Sustiva (TM) (Efavirenz, EFV).
M. AIT-KHALED, A. RAKIK, D. THOMAS, M. TISDALE, J. FALLOON for the CNA2007 International Study Group. Glaxo Wellcome, Stevenage UK, Glaxo Wellcome, RTP NC, NIH, Bethesda MD.

134 Analysis of Possible Predictors of Response to Abacavir (ABC) in Antiretroviral-Experienced Adults; Comparison of Viral Genotype, Viral Phenotype and Patient Treatment History.
R. LANIER*, M. AIT-KHALED, S. MADISON, S. HETHERINGTON, B. WANG, L. DIX AND S LAFON, Glaxo-Wellcome (Corp.) RTP, NC and Stevenage, UK

135 Treatment of Patients (pts.) who Have Virus with Mutations Suggesting Pan-Protease and -Reverse Transcriptase (RT) Drug Resistance.
J.G. MONTOYA*, J.M. SCHAPIRO, A.R. ZOLOPA, T.C. MERIGAN, Center for AIDS Research, Stanford Univ., Stanford, CA, USA.

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M. D. MILLER*, K. E. ANTON, N. A. MARGOT, P. D. LAMY, and A. S. MULATO. Gilead Sci., Foster City, CA.

140 Resistance Mutations as Predictor of Response to Salvage Therapy
P LORENZI, M OPRAVIL, B HIRSCHEL, J-P CHAVE, H SAX, H-J FURRER, TV PERNEGER, L PERRIN, S YERLY and the SHCS Geneva Univ. Hosp., Zurich Univ. Hosp., Ch. Porchat 24, Lausanne; Univ. Hosp. Bern; Switzerland.

248 Reconstitution of M. avium complex (MAC) immune responses after highly active antiretroviral therapy (HAART)
D.V. Havlir, R. Schrier, F. Torriani, K. Chervenak, H. Boom, University of California, San Diego, CA and Case Western Reserve University, Cleveland, OH

249 ACTG 223: An Open, Prospective, Randomized, Study Comparing Efficacy and Safety of Clarithromycin (C) Plus Ethambutol (E), Rifabutin (R) or Both for Treatment (Rx) of MAC Disease in Pts. with AIDS.
C. Benson,* P. Williams, J. Currier, F. Holland, P. Hojczyk, L. Mahon, R. MacGregor, C. Inderlied, K. Nash, C. Flexner, R. Hafner, for the ACTG 223 Protocol Team; UCHSC-Denver, CO, SDAC/Harvard-Boston, MA. UCLA-Los Angeles, CA, SSS-Bethesda, MD, UPenn-Philadelphia, PA, USC-Los Angeles, CA, Johns Hopkins-Baltimore, MD, DAIDS/NIAID-Bethesda, MD

250 Lymphoproliferative Responses to CMV Predict CMV Retinitis Reactivation in Patients who Discontinued CMV Maintenance Therapy.
F. J. TORRIANI*, W. R. FREEMAN, M. KARAVELLAS, C. MACDONALD, D. JEFFREY, D. DURAND, and R. SCHRIER. Univ. of California, San Diego.

251 Incidence and Risk Factors for Developing CMV Retinitis in HIV-Infected Patients Receiving Protease Inhibitor Therapy.
J. Arrizabalaga*, JL Casado, C Tural, P Martin Belda, C Gutierrez, JA Iribarren, K Aguirrebengoa and SpanishCMV-AIDS Study Team

252 Dramatic Rise in Plasma Viremia after CD8+ T-Cell Depletion in SIV-Infected Macaques.
X. JIN, D. BAUER, S. TUTTLETON, S. LEWIN, A. GETTIE, C. IRWIN, J. SAFRIT, L. ZHANG & D. HO. Aaron Diamond AIDS Res. Ctr., The Rockefeller Univ., New York, NY. Emory Univ. Sch. of Med., Atlanta, GA.

253 Evidence for importance of CD8 T cells in controlling SIVmac infection using a CD8 cell depleting mAb in vivo in rhesus monkeys
J.E. SCHMITZ, M.J. KURODA, S. SANTRA, M. DALESANDRO, J. GHRAYEB, D.C. MONTEFIORI, K. TENNER-RACZ, P. RACZ, E. RIEBER, N.L. LETVIN, AND K.A. REIMANN
Beth Israel Deaconess Med. Ctr., Harvard Med. Sch., Boston, MA; Centocor, Malvern, PA; Duke University Med. Ctr., Durham, NC; Institute of Tropical Medicine, Hamburg, Germany, Institute of Immunology, Dresden, Germany.

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D. EVANS, P. JING, D. O'CONNOR, T. ALLEN, J. VENHAM, R. RUDERS-DORF, J. DASILVA, R. BONTROP, C. PAUZA, R. DEMARS, A. HUGHES, D. WATKINS. Present address: Harvard Med. Sch., Southborough, MA; Univ. of Wisconsin, Madison, WI; The Pennsylvania State Univ., University Park, PA; Biomedical Primate Res. Ctr.-TNO, Rijswijk, Netherlands.

256 Containment of breakthrough HIV plasma viremia in the absence of antiretroviral drug therapy is associated with a broad and vigorous HIV specific cytotoxic T lymphocyte (CTL) response.
GM ORTIZ*, X JIN, MA DEMOITIE, S DONAHOE, PJ KUEBLER, S BONHO-EFFER, WM KAKIMOTO, Y CAO, DD HO, M MARKOWITZ, and DF NIXON. The Aaron Diamond AIDS Res. Ctr., The Rockefeller University, New York, NY.

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J. MASCOLA*, M. LEWIS, G. STIEGLER, H. KATINGER, D. HARRIS, D. HAYES, M. LOUDER, T. VANCOTT, S. FRANKEL, C. BROWN, C. SAPAN, M. ROBB, and D. BIRX. Walter Reed Army Inst. of Res. and Henry Jackson Fndn., Rockville, MD, Univ. of Agriculture, Vienna, and NABI, Boca Raton, FL.

258 High RANTES Production from CD4+ Cells Correlates with Slower Progression to AIDS and with CCR5-[DELTA]32 Heterozygocity
W. PAXTON, A. NEUMANN C. BROWN, L. DEUTSCH, S. KANG, L. KOSTRIKIS, D. HO, R. KOUP and S. WOLINSKY. AMC, Amsterdam, Netherlands; Bar-Ilan University, Ramat-Gan, Israel; Nothwestern University, Chicago, IL; Aaron Diamond AIDS Research Center, New York, NY; Southwestern University, Dallas, TX.

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L. MEYER, R. Van RIJ, M. MAGIEROWSKA, M. PRINS, JB. HUBERT, AM. de RODA HUSMAN, R. COUTINHO, I. THEODOROU, H. SCHUITEMAKER, Amsterdam Cohort Studies on AIDS, SEROCO group INSERM U292, Bicetre Hosp., France CLB, Amsterdam, Netherlands URA CNRS 625, Pitie-Salpetriere Hosp., France Amsterdam MHS, Netherlands.

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L. G. KOSTRIKIS*, A. U. NEUMANN, B. THOMPSON, J. F. LEW, K. MCIN-TOSH, H. POLLACK, P. PALUMBO, D. D. HO, and J. P. MOORE. Aaron Diamond AIDS Res., Ctr., New York, NY, Bar-Ilan Univ., Israel, WITS, Baltimore, MD, New York Univ. Med. Sch., New York, NY, and New Jersey Med. Sch., Newark.

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CF BARROGA*, C RASKINO, MC FANGON, J ENGLUND AND SA SPECTOR for the PACTG 152 Team. Univ. of Calif, San Diego, Harvard Sch. of Publ. Health and Univ of Chicago.

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G.A.D. Hardy, N. Imami, B. Gazzard. F.M. Gotch. Dept. of Immunology & Dept. of HIV/GUM, ICSTM, Chelsea & Westminster Hosp., London, UK

324 Long-Term Recovery in CD4+ T Cell Function with Highly Efficient Antiretroviral Therapy.
G. CARVELAIN*, R. TUBIANA, T. S. LI, V. CALVEZ, N. JOUY, M. JOUAN, M. A. VALANTIN, C. OLIVIER, P. M. GIRARD, P. DEBRE, C. KATLAMA, and B. AUTRAN. Hop. Pitie-Salpetriere, Paris, France and Hop. Rothschild, Paris, France.

325 Immune Reconstitution of Advanced HIV Patients (Following HAART)
R. SCHRIER, F. TORRIANI, D. DURAND, D. JEFFREY, L. DREW, J. LALAZARI Univ. of California, San Diego and San Francisco

326 Improved Immunologic Function Correlates with CD4 Rise after Highly Active Anti-Retroviral Therapy (HAART).
H.M. LEDERMAN, C.F. VON REYN, S. BECKER, P. WILLIAMS, J. CURRIER. Johns Hopkins, Baltimore, MD; Dartmouth-Hitchcock Med Ctr, Lebanon, NH ; Harvard Sch Publ Health, Boston, MA; UCLA, Los Angeles, CA

346 Immunological and virological evaluations of the effects of HAART compared to HAART plus an inactivated HIV immunogen after 32 weeks
F. Valentine, V. DeGruttola and the REMUNE 816 Study Team-- NYU Medical Center, New York, NY; Harvard School of Public Health, Boston, MA.

354 Evaluation of Subcutaneous Interleukin-2 Plus Antiretroviral Therapy vs. ARV alone in Patients with HIV-1 Infection and CD4+ Cell Count > 350/mm3.
M. LOSSO*, W. BELLOSO, J. BENETUCCI, P. CAHN, M. LASALA, G. LOPARDO, H. SALOMON, M. SARACCO, S. EMERY, M. ALLENDE, M. LAW, R. DAVEY, and H. C. LANE. Hosp. J.M. Ramos, Buenos Aires, Argentina.

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G. TAMBUSSI*, L. MAGENTA, S. NOZZA, N. GIANOTTI, E. VICENZI, S. GHEZZI, G. POLI, and A. LAZZARIN. San Raffaele Sci.Inst., Milano, Italy.

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H. J. STELLBRINK*, J. VAN LUNZEN, M. WESTBY, E. O'SULLIVAN, N. CAMMACK, A. ADAM, L. WEITNER, S. TUSCHE, B. KUHLMANN, C. HOFFMANN, H. HORST, S. FENSKE, G. SCHMIDT-HARTNACK, S. P. ARIES, K. DALHOFF, C. SCHNEIDER, F. T. HUFFERT, K. TENNER-RACZ, and P. RACZ. Hamburg, Hannover, Kiel, Lubeck, Freiburg, and Roche Welwyn, UK.

357 A Randomized Controlled Multicenter Phase II Trial of Subcutaneous Interleukin-2 (scIL-2) Therapy in HIV-Infected Patients with CD4 Counts 200-500 cells/μL.
R. DAVEY, R. MURPHY, F. GRAZIANO, S. BOSWELL, A. PAVIA, M. CANCIO, J. NADLER, D. SAHNER, A-M. DULIEGE, W CAPRA, C. LANE, and J. KAHN. 1: The CS-L2002 scIL-2 Study Team; 2: Chiron Corp., Emeryville CA.

362 Multiple-dose pharmacokinetics (PK) and tolerability of indinavir (IDV) ritonavir (RTV) combinations in healthy volunteers.
SAAH* AJ, WINCHELL G, SENIUK M, DEUTSCH P. Merck Research Lab, West Point, PA

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D. M. BURGER*, P. W. H. HUGEN, J. M. PRINS, M. E.VAN DE ENDE, P. REISS, and J. M. A. LANGE. Univ. Hosp. Nijmegen, The Netherlands Natl. AIDS Therapy Evaluation Ctr., Univ. of Amsterdam, The Netherlands and Univ. Hosp. Rotterdam, The Netherlands.

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W. ROZENBAUM*, N. DELPHIN, C. KATLAMA, P. MASSIP, M. BENTATA, J. P. MAMET, and G. STURGE. Rothschild Hosp. and, Pitie Salpetriere, Paris, France, Purpan Hosp., Toulouse, France, Avicenne Hosp., Bobigny, France, and Glaxo Wellcome, Inc., Paris, France.

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P. VERNAZZA*, C. KATLAMA, B. CLOTET, A. PLETTENBERG, L. GOH, A. CUTRELL, and S. PURDON. Kantonsspital, St Gallen, Switzerland, Pitie Salpetriere Hosp., Paris, France, Hosp. Germans Trias i Pujol, Barcelona, Spain, Allgemeines Krankenhaus St. George, Hamburg, Germany, and Glaxo Wellcome, London, UK.

381 Substitution of NNRTI for Protease Inhibitor in Patients on Combination Therapy with Undetectable Plasma Viral Loads
F RAFFI*, B BONNET, V FERRE, S LEAUTEZ, V RELIQUET, C ALLAVENA, S AUGER, E BILLAUD. Univ. Hosp., Nantes, France.

382 Durability of Response of Efavirenz (SUSTIVA, EFV)-Containing Regimens: Report of the Post-Control Period Results of Studies with EFV.
DJ MANION*, E FAULKNER, TD SAXTON, DF LABRIOLA, NM RUIZ, DuPont Pharmaceuticals Co, Wilmington, DE.

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DJ MANION*, DF LABRIOLA, NM RUIZ, DuPont Pharmaceuticals Company, Wilmington, DE

388 Treatment with Indinavir (IDV), Zidovudine (ZDV) and Lamivudine (3TC): Three-year follow-up.
R. GULICK, J. MELLORS, D. HAVLIR, J. ERON, F. VALENTINE, D. McMAHON, C. GONZALEZ, L. JONAS, A. MEIBOHM. J. CHODAKEWITZ, R. ISAACS, D. RICHMAN. Cornell Univ., Univ. of Pitts./VAMC, Univ. of Cal., San Diego, Univ. of North Carolina, Chapel Hill, New York Univ., Merck Research Labs., West Point, PA.

389 Quadruple Therapy with Saquinavir-Soft Gelatin Capsules (SQV-SGC) plus Nelfinavir (NFV) Versus Triple Therapy with Either SQV-SGC or NFV in Patients with Antiretroviral Experience or High Baseline Viral Load
M JOHNSON* ON BEHALE OF THE SPICE (NV15436) STUDY GROUP Royal Free Hospital, London, UK

390 FORTOVASE BID Regimens in HIV-1 Infected Patients: Combination with 2 Nucleoside Analogs or with Nelfinavir plus 1 NA.
L. SLATER, M. SENSION, J. FEINBERG, R. POBLETE, P. SIEMON-HRYCZYK, R. PILSON, and S. PALLEJA. Oklahoma Univ. Hlth. Sci. Ctr., Oklahoma City, OK, North Broward Hosp. Dist., Fort Lauderdale, FL, Univ. of Cincinnati Med. Ctr., Cincinnati, OH, NJRCI, Newark, NJ, Roche Labs Inc., Nutley, NJ.

392 60-week virologic responses to a ritonavir/saquinavir containing regimen in patients who had previously failed nelfinavir
P. TEBAS, A. K. PATICK, E. KANE, M. KLEBERT, J. SIMPSON, B. ATKINSON, J. ISAACSON, W.G.POWDERLY, K. HENRY. Washington Univ. Sch. of Medicine, St. Louis Missouri, Agouron Pharmaceuticals, Inc, San Diego, California and University of Minnesota, Minneapolis-St. Paul, Minnesota

399 A pilot randomized comparative study of Stavudine (d4T) - Didanosine (ddI)+ Nevirapine (NVP) with or without Hydroxyurea (HU) in Primary HIV Infection (PHI).
C Zala*, H Salomon, A Gun, D Rouleau, S Pampurro, H Perez, P Cahn, JSG Montaner. Fundacion Huesped, University of Buenos Aires, Argentina, Universite de Montreal, Quebec and University of British Columbia, Vancouver, Canada.

401 Tailoring Drug Treatments with the Use of Hydroxyurea.
F. LORI*, E. ROSENBERG, H. JESSEN, J. LIEBERMAN, D. FINZI, E. SEMINARI, R. MASERATI, R. F. SILICIANO, B. WALKER, and J.LISZIEWICZ. RIGHT, Georgetown Univ.,Washington, DC and Policlinico S Matteo, Pavia, Italy, Massachusetts Gen. Hosp., Boston, Jessen

Praxis, Berlin, Germany, The Ctr. for Blood Res., Boston, MA, and Johns Hopkins Univ., Baltimore, MD.

402 Phase I/II Dosing Study of Once-Daily Hydroxyurea (HU) Alone vs Didanosine (ddI) Alone vs ddI + HU.
I. FRANK, H. BOUCHER, S. FISCUS, C. FLEXNER, F. VALENTINE, R. GULICK, L. FOX, AND J. ERON FOR THE ACTG 307 TEAM. Univ of Penn, Philadelphia, PA, Harvard Univ., Brookline, MA., UNC, Chapel Hill, NC, Johns Hopkins Univ., Baltimore, MD, NYU, New York, NY, NIAID, Bethesda, MD.

403 The Prometheus Study: Double Protease Inhibitor (PI) Treatment Only is Unable to Suppress Detectable Viral Load in the CSF.
E GISOLF, S JURRIAANS, M VAN DER ENDE, P PORTEGIES, R HOETELMANS AND S DANNER. 1 National AIDS Therapy Evaluation Ctr; 2 Academic Medical Center, Amsterdam; 3 Academic Hosp, Rotterdam; 4 Slotervaart Hosp, Amsterdam, the Netherlands.

405 Discordant HIV-1 RNA Decay in CSF versus Plasma Following Initiation of Antiretroviral Therapy: A Prospective Ultra-Intensive CSF Sampling Study.
DW HAAS*, P SPEARMAN, B JOHNSON, VL HARRIS, R DONLON, GR WILKINSON, LA CLOUGH, RA GROSSO, MR STEVENS. Vanderbilt Univ. Sch. of Med., Nashville, TN and Bristol-Myers Squibb Co.

407 Levels of Serum and Cerebrospinal Fluid (CSF) Indinavir (IDV) and HIV RNA in HIV-Infected Individuals.
S. L. LETENDRE*, E. CAPARELLI, R. J. ELLIS, D. DUR, and J. A. MCCUTCHAN. Univ. of California, San Diego.

435 Hypercholesterolemia in Children Treated with HIV Protease Inhibitors.
D. C. WATSON* and J. J. FARLEY. Univ. of Maryland, Baltimore.

455 A 24 Month Follow-up of Cytomegalovirus Retinitis without Secondary Prophylaxis Following Highly Active Antiretroviral Therapy.
C. TURAL*, G. SIRERA, J. ROMEU, A. BONJOCH, A. JOU, D. ANDREU, L. RUIZ, A. ARNO, R. PAREDES, and B. CLOTET. Hosp. Univ. Germans Trias i Pujol. Barcelona, Spain.

489 ACTG 364: Virologic Efficacy of Nelfinavir (NFV) and/or Efavirenz (EFZ) in Combination with New Nucleoside Analogs in Nucleoside Experienced Subjects (subj).
M. ALBRECHT*, D. KATZENSTEIN, R. BOSCH, S. LIOU, S. HAMMER for the ACTG 364 Study Team, NIAID Sponsored AIDS Clinical Trials Group, Bethesda, MD

490 Randomized Trial of Abacavir (ABC) & Nelfinavir (NFV) in Combination with Efavirenz (EFV) & Adefovir Dipivoxil (ADV) as Salvage Therapy in Patients with Virologic Failure Receiving Indinavir (IDV).
S. HAMMER, K. SQUIRES, V. DEGRUTTOLA, M. FISCHL, R. BASSETT, L. DEMETER, K. HERTOGS, B. LARDER & THE ACTG 372B STUDY TEAM, NIAID Sponsored AIDS Clinical Trials Group, Bethesda, MD & VIRCO, Mechelen, Belgium.

493 Virologic Failure, Resistance and Plasma Drug Measurements in Induction Maintenance Therapy Trial (Anrs 072, Trilege).
D DESCAMPS*, G PEYTAVIN, V CALVEZ, P FLANDRE, V MEIFFREDY. F RAFFI, G PIALOUX, JP ABOULKER, F. BRUN-VEZINET and the Trilege study group, France.

496 Effect of Interleukin-2 in Diminution of a Pool of Latently Infected, Resting CD4 T Cells in HIV-1 Infected Patients Receiving Highly Active Antiretroviral Therapy
T.-W. CHUN*, D. ENGEL, S. MIZELL, J. METCALF, C. HALLAHAN, J. KOVACS, R. DAVEY., M. DYBUL, J. MICAN, C. LANE, AND A. FAUCI, LABORATORY OF IMMUNOREGULATION, NIAID, NIH, BETHESDA, MD 20892.

499 HIV-1 Entry into Macrophages through CXCR4 or CCR5: Two Mechanisms of Dual-Tropism for HIV-1 Primary Isolates
Y. YI*, D. A. WILLIAMS and R.G. COLLMAN. University of Pennsylvania, Philadelphia, PA

505 Enhancement of Human Immunodeficiency Virus Type 1 Infection by RANTES Is Independent of the Mechanism of Virus-Cell Fusion
C. GORDON, M. MUESING, A. E. I. PROUDFOOT, C. A. POWER, J. P. MOORE AND A. TRKOLA The Aaron Diamond AIDS Res. Ctr., New York, NY, New York Univ. Sch. of Med., New York, NY, The Rockefeller Univ., New York, NY, Serono Pharmaceutical Res. Inst., Geneva, Switzerland

507 Recruitment of Cyclin T/P-TEFb is Necessary and Sufficient for Transactivation of the HIV-1 long terminal repeat.
P. D. BIENIASZ*, T. A. GRDINA, H. P. BOGERD, and B. R. CULLEN. Howard Hughes Med. Inst., Duke Univ. Med. Ctr., Durham, NC.

508 Role of Matrix in HIV-1 Replication
H. REIL, A. BUKOVSKY, J. PAILLART, T. DORFMAN, and H. GOTTLINGER Dana-Farber Cancer Institute, Boston, MA

509 HIV-1 Nef Activates PAK Kinase in Infected Human Primary Macrophages.
A. BROWN*, E. SAWAI, and C. CHENG-MAYER. Aaron Diamond AIDS Res. Ctr., New York, NY and Univ. of California Davis.

510 A Dileucine-Based Sorting Motif within Nef of HIV-1 is Required for Optimal Viral Infectivity and CD4 Downregulation.
H. M. CRAIG*, T. R. REDDY, M. W. PANDORI, and J. C. GUATELLI. Univ. of California, San Diego and San Diego VA Med. Ctr., La Jolla, CA.

511 Interaction of HIV-1 Vpr with the Cell Cycle.
W. C. GOH*, H. PIWNICA-WORMS, and M. EMERMAN. Fred Hutchinson Cancer Res. Ctr., Seattle, WA and Washington Univ. Sch. of Med., St. Louis, MO.

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W. C. GOH*, H. PIWNICA-WORMS, and M. EMERMAN. Fred Hutchinson Cancer Res. Ctr., Seattle, WA and Washington Univ. Sch. of Med., St. Louis, MO.

513 Deletions Within the Dimerization Initiation Site of HIV-1 Can be Compensated by Three Distinct Point Mutations Within Gag.
C. LIANG*, L. RONG, E. CHERRY, and M. A. WAINBERG. McGill AIDS Ctr./Jewish Gen. Hosp., Montreal, Quebec, Canada.

521 Central Role of CCR5 as a Coreceptor in Tissue Infection by HIV-1
S.Y. CHAN, R.F. SPECK, C. POWER, S.L. GAFFEN, B.CHESEBRO, and M.A. GOLDSMITH Gladstone Inst. of Virology and Immunology and Univ. of California San Francisco, San Francisco, CA; Univ. of Calgary, Calgary, Alberta; Lab. of Persistent Viral Diseases, Rocky Mountain Labs, NIAID, Hamilton, Montana; and Dept. of Medicine, School of Medicine, University of California, San Francisco, CA.

562 Immunological and Virological Characterization of Individuals with Long-Term Non-progressive HIV-1 Infection in a Hemophilia Cohort.
T. GREENOUGH*, D. BRETTLER, F. KIRCHHOFF, L. ALEXANDER, R. DESROSIERS, M. SOMASUNDARAN, K. LUZURIAGA, and J. L. SULLIVAN. Univ. of Massachusetts Med. Sch., Worcester, Univ.of Erlangen-Nuernberg, Germany, and NE Reg. Primate Res. Ctr., Southborough, MA.

565 Polymorphisms of Genes in HLA Class I and CCR Regions Strongly Predict HIV Viral Load 1 Year after Seroconversion in the Multicenter AIDS Cohort Study (MACS).

RA KASLOW, M CARRINGTON, J TANG, L YEE, C ENGER, J MELLORS Univ of Alabama at Birmingham, Birmingham AL, FCRDC, Frederick MD, Johns Hopkins Univ, Baltimore MD, Univ of Pittsburgh, Pittsburgh PA for the MACS.

568 CCR5 and SDF-1 Polymorphism in HIV-1 Infected Individuals.
C. BALOTTA*, P. BAGNARELLI, M. VIOLIN, S. CORVASCE, L. PAPAGNO, R. MAZZUCCHELLI, C. RIVA, R. ELLECA, M. CLEMENTI, M. GALLI, and M. MORONI. Inst. of Infectious and Tropical Diseases, Univ. of Milan, Italy, Inst. of Microbiology, Univ. of Ancona, Italy, and Univ. of Trieste, Italy.

580 HIV-1 Viral Protein R Mediates Enhanced Replication in Primary Human CD4+ T-cells by Arresting Cells in the G2 Phase of the Cell Cycle.
R. GUMMULURU* and M. EMERMAN. Fred Hutchinson Cancer Res. Ctr., Seattle, WA.

581 Phosphorylation of HIV-1 Vpr and Effect on Vpr Biological Functions.
Y. ZHOU* and L. RATNER. Washington Univ. Sch. of Med., St. Louis, MO.

593 Synthesis and Anti-HIV Activity of 2'-Fluoro-2',3'-unsaturated L-Nucleoside (L-d4N) Analogs
K. Lee, Y.S. Choi, R.F. Schinazi and C. K. Chu Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, The University of Georgia, Athens, GA 30602 and Emory University School of Medicine/VA Medical Center, Atlanta, GA 30033.

594 Antiviral Activity and Resistance Profile of Phosphazid - A Novel Prodrug of AZT.
J. MACHADO, C. TSOUKAS, H. SALOMON, A. KRAYEVESKY, and M. A. WAINBERG*. McGill AIDS Ctr., McGill Univ., Montreal, Quebec, Canada and Inst. Biochemical Res., Moscow, Russia.

595 Antiretroviral Activity, Safety and Metabolism of BCH-10652, a New Nucleoside Analogue.
R.F. RANDO, J.-M. DE MUYS, C. LOCAS, S. TYMS, C. FORTIER. BioChem Pharma, Montreal, Canada; MRC Collaborative Centre, Mill Hill, London, UK.

596 Single-dose Pharmacokinetics (PK) of BCH-10652 in Healthy, Adult Volunteers.
P. SMITH, C. BALLOW, A. FORREST, D. MARTIN, C. FORTIER, L. PROULX. SUNY-Buffalo School of Pharmacy and Clinical PK Lab., Buffalo, NY; PharmaResearch Corp., Morrisville, NC; BioChem Pharma, Montreal, Canada.

597 Novel mutations in HIV-1 reverse transcriptase selected for by 2',3'-dideoxy, 2',3'-didehydro-fl-5-fluorocytidine, a potent inhibitor of HIV-1.
J HAMMOND, R SCHINAZI, S SCHLUETER-WIRTZ, J MELLORS. Univ. of Pittsburgh/VA Med. Ctr., Pittsburgh, PA ; Emory Univ./ VA Med. Ctr. Atlanta. GA

599 GW420867X: A Novel Quinoxaline-Class NNRTI of HIV-1 with Improved Antiviral Properties in the Presence of Human Serum and its Components
JORG-PETER KLEIM, VIKKI BURT, MICHAEL MAGUIRE, PETER MUTCH, RICHARD J. HAZEN, AND MARTY ST CLAIR Glaxo Wellcome Research and Development, Stevenage and Ware, UK, Research Triangle Park, NC, USA.

600 NNRTI GW420867X: Comparative Evaluation of the In Vitro Resistance Profile
JORG-PETER KLEIM, VIKKI BURT, MICHAEL MAGUIRE, ROB FERRIS, RICHARD J. HAZEN, GACIE ROBERTS, AND MARTY ST CLAIR Glaxo Wellcome Research and Development, Stevenage, UK, and Research Triangle Park, NC, USA.

602 (-)-Calanolide B - A Novel and Naturally-Occurring Non-Nucleoside Reverse Transcriptase Inhibitor of HIV-1
T. JENTA, D. SOEJARTO, R. BUCKHEIT, E. ARNOLD, K. SCHWEIKART and J. COVEY. Sarawak MediChem Pharmaceuticals, Lemont, IL. Uni. Illinois Chicago, Chicago, IL. Southern Res. Inst., Birmingham, AL. Rutgers Uni., Piscataway, NJ. NCI, Rockville, MD.

603 Resistance Profile And Drug Combination Studies of an HIV-1 Protease Inhibitor BMS-232632
Y. GONG, B. ROBINSON, R. ROSE, K. RICCARDI, C. DEMINIE, D. STOCK, T. SPICER, F. DJANG, J. CROSS, R. COLONNO and P-F. LIN* Bristol-Myers Squibb Company, Wallingford, CT

604 BMS-232632: Single and Multiple Oral Dose Safety and Pharmacokinetic Study in Healthy Volunteers.
E. M. O'MARA*, J. SMITH, S. J. OLSEN, T. TANNER, A. E. SCHUSTER, and S. KAUL. Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ and Simbec Res. Ltd., Merthyr Tydfil, UK.

606 Clinical Safety and Pharmacokinetics of (+)-Calanolide A, A Naturally Occurring NNRTI, in Normal Healthy and HIV-Infected Volunteers
J. RUCKLE, J. GILTNER, T. CREAGH, B. DUTTA, D. TOLBERT, Z.-Q. XU* Sarawak MediChem Pharmaceuticals, Inc., Lemont, IL 60439

608 AR177 Inhibits HIV-1 Entry in vivo.
C. STODDART*, M. MORENO, V. LIN-QUIST-STEPPS, C. BARE, M. BOGAN, T. WALLACE, and J. M. MCCUNE. Gladstone Inst. of Virology and Immunology, Univ. of California, San Francisco, and Aronex Pharmaceuticals, Inc., The Woodlands, TX.

609 A more potential CXCR4-dependent inhibitor, T140
Younong Xu, Hirokazu Tamamura, Xiaoyan Zhang, Nobutaka Fujii, Takashi Uchiyama, and Toshio Hattori Institute for Virus Research Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

610 Chemokine CXCR-4 Receptor Blocker, AMD-3100: Clinical and Pre-clinical Studies of Pharmacokinetics and Safety.
C HENDRIX, C FLEXNER, R MACFARLAND, C GIANDOMENICO, SCHWEITZER, G HENSON Johns Hopkins University School of Medicine, Baltimore, MD, USA; AnorMED, Langley, BC, Canada; Novartis, Ltd., Basil, Switzerland.

611 HIV-1 Selection in Response to Inhibition of Virus Fusion and Entry
X. WEI, M. KILBY, S. HOPKINS, M. SAAG, G. SHAW, Howard Hughes Inst., Univ. of Alabama at B'ham, AL, Trimeris, Inc., Durham, NC

612 HIV-1 Replication Kinetics After Perturbation of de novo Infection by T-20 A Potent Fusion Inhibitor.
A. DUSEK* and S. HOPKINS. Trimeris, Inc. Durham, NC.

613 CCR5 Antagonists Either Inhibit HIV-1 Infection of hu-PBL-SCID Mice or Select for CXCR4-Using Variants.
D. MOSIER*, G. PICCHIO, R. GULIZIA, R. SABBE, P. POIGNARD, R. OFFORD, D. THOMPSON, and J. WILKEN. The Scripps Res. Inst., La Jolla, CA, Ctr. Med. Univ., Geneva, Switzerland, and Gryphon Sci., S. San Francisco, CA.

614 Safety and Efficacy of FP-21399 a Novel Fusion Inhibitor- Results of a 48 wk Phase II Study.
J. C. GATHE JR*, C. SHAPIRO, S. SCHRADER, C. MAYBERRY, T. DAHL, and F. WONG. Houston Clin. Res. Network, TX and Lexigen Pharm., Lexington, MA.

615 In Vitro Inhibition of HIV-1 in Peripheral Blood Mononuclear Cells by Met-SDF1.
S. RUSCONI *, D. P. MERRILL, O. O. YANG, and M. S. HIRSCH. Massachusetts Gen. Hosp. and Harvard Med. Sch., Boston, MA.

616 A Novel Hybrid Synthetic Peptide Inhibitor of HIV-1, SIV, and HIV-2 Fusion and Infection In Vitro.
SHAWN BARNEY*, KELLY GUTHRIE, DIANA DAVIS, LAURI NEWMAN, M. ROSS JOHNSON, and DENNIS M. LAMBERT. Trimeris, Inc., Durham, NC.

617 Potent Inhibition of HIV-1 Replication In Vitro and In Vivo by a Synthetic Hybrid Peptide Inhibitor of HIV-1, SIV, and HIV-2 Fusion.
M. USSERY*, O. WOOD, D. BROUD, M. BACHO, S. KUNDER, S. VONA, S. BALA, C. NIELSEN, K. GUTHRIE, D. DAVIS, D. LAMBERT, and S. BARNEY. FDA, Rockville, MD, and Trimeris, Inc., Durham, NC.

618 A Phase I Dose Escalation Trial of PRO 542, A Novel Inhibitor of HIV-1 Entry.
J. JACOBSON, I. LOWY, T. O'NEILL, W. OLSON, and R. ISRAEL. The Mount Sinai Medical Center, New York, NY 10021 and Progenics Pharmaceuticals, Inc., Tarrytown, NY 10591

624 Second Placebo-Controlled Study in Naive Individuals Confirms the Role of Delavirdine in Higly Active Antiretroviral, Protease-Sparing Treatment.
R. WOOD*, D. A. HAWKINS, G. MOYLE, W. DE CIAN, A. INGROSSO, and C. GREENWALD. Somerset Hosp., Cape Town, South Africa, Chelsea and Westminster Hosp., London, UK, Pharmacia & Upjohn, Italy, and Pharmacia & Upjohn, USA.

625 Durable Activity of Ziagen (Abacavir, ABC) Combined with Protease Inhibitors (PI) in Therapy Naive Adults.
MELLORS J, LEDERMAN M, HAAS D, HORTON J, HAUBRICH R, STANFORD J, COONEY E, LAFON S, KELLEHER D. U of Pittsburgh /VA Medical Center Pittsburgh PA, CWRU Cleveland OH, Vanderbilt Univ Nashville TN, Carolinas Med Center Charlotte NC, UCSD SanDiego CA KCARC Kansas City MO, Yale Univ NewHaven CT, Glaxo Wellcome RTP NC

626 Combination Ziagen (Abacavir, ABC)/Amprenavir (141, APV-USAN) Therapy in HIV-1 Infected Antiretroviral Naive Subjects with CD4 Counts >400 cells/µl and Plasma HIV-1 RNA >5000 copies/mL.
P-A BART, GP RIZZARDI S GALLANT, A CHAPUIS, C WELBON, C GRAZIOSI, J-P CHAVE, J-M CORPATAUX, J-Y MEUWLY, P MEYLAN, I VAFIDIS, H STEEL, W SPREEN, H McDADE, A LAZZARIN, G PANTALEO, CHUV. Lausanne, Switzerland; Clin. La Source, Lausanne, Switzerland; GlaxoWellcome, London, UK; GlaxoWellcome, Inc., RTP, USA; HSR, Milan, Italy.

628 An Open Randomized Study Comparing d4T plus ddI and Nevirapine (QD) vs d4T plus ddI and Nevirapine (BID) in Antiretroviral Naive Chronic HIV-1 Infected Patients in Very Early Stages (Spanish SCAN Study)
F GARCIA*, H KNOBEL, M.A. SAMBEAT, J RCMEU, F SEGURA, M ARANDA, D DALMAU, MM ALONSO, J M GATELL, J M MIRO for the Spanish SCAN Study.

631 Efficacy and Safety of BID Firstline Ritonavir/Indinavir Plus Double Nucleoside Combination Therapy in HIV-infected Individuals
J.K. Rockstroh*, Bergmann F, Wiesel W, Rieke A, Nadler M, Knechten H and the German Ritonavir/Indinavir Study Group. Univ. of Bonn, Humboldt Univ. Berlin, Private Practice Cologne, Hosp. Kemperhof Koblenz, Private Practice Berlin, Private Practice Aachen, Germany.

632 The VIRGO Trial: d4T/ddI (qd)/nevirapine (bid or qd) in Antiretroviral-Naive HIV-1-Infected Patients - a Convenient and Potent Regimen.
F RAFFI*, V RELIQUET, C HASCOET, C ARVIEUX, M GARRE, JM BESNIER, P PERRE, W ROZENBAUM, JM MOLINA, G RAGUIN, C FRANCOIS, S AUGER and The VIRGO Study Team, Hosp. of Nantes, Brest. Saint-Brieuc, Rennes, Tours, La Roche sur Yon, Nancy; Rothschild Hospital, Paris, Saint Louis Hospital, Paris, and Croix St Simon, Paris, France.

633 Ozcombo I: Control of HIV Replication in Treatment Naive Patients in a Randomised Trial of HAART
A. CARR, J. HUDSON, J. HOY*, J. CHUAH, and M. FRENCH for the Ozcombo I investigators network NCHECR, UNSW, Sydney, Australia.

634 Initial HIV-1 Clearance Rate in Antiretroviral Naive Patients After Antiretroviral Therapy With D4T plus DDI and either NVP, IDV, or 3TC.
R. VAN HEESWIJK*, A. LIPNIACKI, P. NOWAK, R. HOETELMANS, M. KWAKKELSTEIN, R. VAN LEEUWEN, A. HORBAN, J. BEIJNEN, J. LANGE, and A. PIASEKSUP. Slotervaart Hosp., Amsterdam, The Netherlands, AIDS Diagnosis and Therapy Ctr., Warsaw, Poland, Boehringer Ingelheim, Alkmaar, NATEC, Amsterdam, The Netherlands.

635 Remarkably Sustained Virologic Response After Indinavir Addition to Suboptimal AZT/3TC and d4T/3TC Therapy: 72 Weeks Follow-Up.
N. FOUDRAINE*, G. WEVERLING, S. JURRIANNS, M. ROOS, P. REISS, and J. LANGE. Academic Med. Ctr., Amsterdam, CLB, Sanguin Blood Supply Fndn., Amsterdam, The Netherlands.

636 The long term response to combination therapy commenced early in HIV infection: 3 year follow-up. What's happened since Vancouver?
M. MARKOWITZ, K. TENNER-RACZ, L. ZHANG, A. HURLEY, B. RAMRATNAM, Y. CAO, D. BODEN, M. DURAN, C. FARTHING, P. RACZ, D.D. HO. Aaron Diamond AIDS Res. Ctr, NY, NY; Bernard-Nocht Inst. Hamburg, GER ; AIDS HealthCare, LA, CA

637 Viral suppression and CD4-cell recovery in patients with primary HIV-1 infection treated with HAART
V.A. SORAVIA-DUNAND, R.D. SAN MILLAN, S. YERLY, G. SCHOCKMEL, J-P. CHAVE, A. CHARVIER, C. FAGART, J.-F. BALAVOINE, B. HIRSCHEL, L. PERRIN Geneva Univ. Hosp., Geneva, Switzerland; Lausanne, Switzerland; Annecy Hosp. Ctr., France.

639 Potent, Durable Combination Therapy with Abacavir, Amprenavir, and ZDV/3TC in Subjects Acutely & Chronically Infected with HIV-1.
R. KOST, Y. CAO, L. ZHANG, A. HURLEY, S. MONARD, M. ROGERS, L. SMILEY, D. HO, M. MARKOWITZ. Aaron Diamond AIDS Research Center, The Rockefeller University, NY, Glaxo Wellcome, RTP, NC.

641 Diagnosis and prediction of HIV protease inhibitor (PI)-induced lipodystrophy and impaired glucose tolerance

642 Frequency of Lipodystrophy and Factors Associated with Glucose/Lipid Abnormalities in a Cohort of 650 Patients Treated by Protease Inhibitors.
S. GHARAKHANIAN*, Y. SALHI, T. H. NGUYEN, N. ADDA, S. CATRIX, C. VIGOUROUX, J.CAPEAU, and W. ROZENBAUM. Rothschild Hosp., Paris, France.

644 Prevalence And Risk Factors For Hyperglycemia, Dyslipidemia, And Coronary Disease Among Hiv-Infected Patients On Initial Protease Inhibitor Therapy
D. LEE* and W.C. MATHEWS University of California, San Diego Medical Center, San Diego, CA

653 A Syndrome of Lipodystrophy in Patients Receiving a Stable Nucleoside-Analogue Therapy.
T. SAINT-MARC*, I. POIZOT-MARTIN, M. PARTISANI, J. FABRE, J.L. TOURAINE, Dept. of Transplantation and Clin. Immunology - E. Herriot Hosp. - 69437 LYON cedex 03 - FRANCE.

654 Lypodystrophy Syndrome (LS) In Patients On Reverse Transcriptase Inhibitors.
S MADGE*, S KINLOCH-DE LOES, M TYRER, MA JOHNSON Royal Free HIV Unit, The Royal Free Centre for

656 Increased Morbidity from Severe Coronary Heart Disease in HIV-Patients Receiving Protease Inhibitors.
A. JUETTE*, B. SALZBERGER, C. FRANZEN, K. ROEMER, V. DIEHL, G. FAETKENHEUER. Dept. of Med. I, Univ. Hosp., Cologne, Germany.

657 Do Protease Inhibitors Increase the Risk for Coronary Heart Disease Among HIV Positive Patients?
D. KLEIN*, S. SIDNEY, L. HURLEY, and C. IRIBARREN. Kaiser Permanente Med., Haywood, CA.

658 No Association Observed Between Indinavir Therapy for HIV/AIDS and Myocardial Infarction in 4 Clinical Trials with 2,825 Subjects
P COPLAN*, A NIKAS, A SAAH, M NESSLY, L DOLL, R LEAVITT, J BENSON, H GUESS. Merck Research Laboratories, Blue Bell, PA 19422.

659 Relationship Between Body Fat Distribution, Lipoprotein Levels and Fasting Insulin in HIV+ Women Treated with Protease Inhibitors (PI).
L BAUSSERMAN*, M FLYNN, R DICKENSON, M MILENO, C CARPENTER. Brown Univ./The Miriam Hosp., Providence, RI.

661 Association of Diabetes and Protease Inhibitor Use In A Large Natural History Cohort of HIV+ Women.
J. JUSTMAN*1, A. DANCFF2, L. BENNING3, E. ROBISON4, K. WEBER, H. MINKOFF, A. LEVINE, M. YOUNG, R. GREENBLATT, K. ANASTOS5 Women's Interagency HIV Study (WIHS), 1,2Bronx-Lebanon Hosp. Ctr.,Bronx NY, 3John: Hopkins Univ., Baltimore MD, 4Montefiore Med. Ctr., Bronx NY, 5Catholic Med. Ctr., Jamaica NY

663 Women First: Durable Response with Dual Protease Inhibitor Therapy Without Significant Elevations in Lipids.
J. CURRIER*, R. CLARK, K. SQUIRES, M. TILL, P. GRIEGER, C. ZORILLA, M. GERSTEN, N. WILCOX, M. SCHULTZ, and M. ZHANG. Univ. of Southern California, Los Angeles, Louisiana State Univ., New Orleans, Univ. of Alabama at Birmingham, Northwestern Univ., Chicago, IL, Univ. of Puerto Rico, and Agouron Pharm., La Jolla, CA.

668 Reversibility of protease inhibitor (PI) lipodystrophy syndrome on stopping PIs or switching to nelfinavir.
A CARR*, A THORISDOTTIR, K SAMARAS, GR KAUFMANN, DJ CHISHOLM, DA COOPER. St.Vincent's Hospital, Garvan Institute of Medical Research, National Centre in HIV Epidemiology and Clinical Research. Sydney, Australia.

669 Management of Indinavir-associated metabolic changes by substitution with Efavirenz in virologically controlled HIV+ persons

671 EXPERIENCE WITH THE NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) GUIDELINES FOR THE IDENTIFICATION AND TREATMENT OF PROTEASE INHIBITOR RELATED LIPID ABNORMALITIES: RESULTS OF A PROSPECTIVE STUDY
K Henry*1,3, H Melroe1, J Huebesch2, J Kopaczewski1, and J Simpson1. HIV Program1 and Lipid Program2, Regions Hospital and the *University of Minnesota3, St. Paul. MN, USA.

672 Effects of Metformin on Insulin Resistance and Central Adiposity in Patients Receiving Effective ProteaseInhibitor (PI) Therapy.

673 Effects of the PPAR-g Activator Troglitazone on Protease Inhibitor Associated Peripheral Insulin Resistance.
R. K. WALLI*, G. M. MICHL, J. R. BOGNER, and F. D. GOEBEL. Ludwig-Maximilians-Univ., Munich, Germany.

674 Incidence of Body Habitus Changes In a Cohort of 725 HIV-Infected Patients.
D. DIETERICH*, R. AYMAT, J. BRAUN, M. MULLEN, A. MCMEEKING, K. WEISZ, S. KREISWIRTH, B. O'BRIEN, K. LAWSON, P. HERGENROEDER, and R. TIRELLI. New York Univ. Med. Ctr., St. Vincent's Med. Ctr., Cabrini Med. Ctr. and Liberty Med. LLP, New York, NY. A CARR*, K SAMARAS, A THORISDOTTIR, GR KAUFMANN, DJ CHISHOLM, DA COOPER. St.
HIV Medicine, Pond Street, London NW3 2QG UK T. SAINT-MARC*, J.L. TOURAINE. E. Herriot Hosp - 69437 LYON -FRANCE

675 The Effect of Recombinant Human Growth Hormone on Protease-Inhibitor-Associated Fat Maldistributionv Syndrome.
R. TORRES*1 and K. UNGER2. 1Bentley-Salick Med. Practice, New York, NY and 2New York Univ., New York,NY. G MOYLE*, C BALDWIN, N DENT & B GAZZARD Chelsea & Westminster Hospital

692 The Risk for Pneumocystis carinii Pneumonia (PCP) and Disseminated Nontuberculous Mycobacteriosis (dMb) After an Antiretroviral Therapy (ART) Associated Increase in the CD4+ T-lymphocyte Count
M. DWORKIN*, D. HANSON, J. JONES, J. KAPLAN, and the ADULT/ADOLESCENT SPECTRUM OF HIV DISEASE PROJECT (ASD). CDC,Atlanta, GA.

L1 Antiretroviral Therapy in Adults
Stefano Vella MD, Istituto di Sanit‡, Rome, Italy.

L2 Pediatric Antiretroviral Therapy
K. Luzuriaga, Univ. of Mass., Med. School, Worcester.

L3 HIV Tat and Rev: What They Do and How They Do It
B.R. Cullen, Howard Hughes Medical Inst., Duke Univ. Med. Center, Durham, N.C.

L5 Structure and Assembly of the HIV-1 Capsid
S. Li, B.K. Ganser, V.Y. Klishko, J.T. Finch, C.P. Hill, W.I. Sundquist, Dept. of Biochemistry, University of Utah, Salt Lake City, Utah, Structural Studies Division, MRC Laboratory of Molecular Biology, Hills Road, Cambridge, UK

L6 Abstract not submitted

LB10 [Late Breaker] The Spectrum and Frequency of Reduced Antiretroviral Drug Susceptibility With Primary HIV Infection in the United States.
S. LITTLE *, E DAAR, P KEISER,, R D'AQUILA, E CONNICK, N HELLMANN, C PETROPOULOS, R KOUP, E ROSENBERG, B WALKER, and D RICHMAN. Univ. California, San Diego, CA, Cedar-Sinai Med. Ctr., Los Angeles, CA, Univ. Texas, Dallas, TX, Massachusetts Gen. Hosp., Boston, MA, Univ. Colorado, Denver, CO, ViroLogic, Inc., South San Francisco, CA

LB11 [Late Breaker] Selection of Protease Resistance Mutations in Semen.
MP DePASQUALE*, N KARTSONIA, J MARTINEZ-PICADO, J ERON, S FISCUS, J SCHOCK, L SMEATON, R GULICK, R MURPHY, R D'AQUILA. Mass. General Hosp. & Harvard Univ, Boston, MA; Univ of North Carolina, Chapel Hill, NC; Cornell Univ, NY, NY; Northwestern Univ, Chicago IL; ACTG 347/850 Teams

LB12 [Late Breaker] Viral rebound in the presence of indinavir without protease inhibitor resistance.
D. HAVLIR *, N. HELLMANN, C. PETROPOULOS, J. WHITCOMB, A. COLLIER, M. HIRSCH, P. TEBAS, and D. RICHMAN. UCSD, San Diego CA, ViroLogic, South SF, Univ of WA, Seattle, Harvard, Boston, and Washington Univ, St. Louis

LB 13 [Late Breaker] Safety, Pharmacokinetics, and Antiviral Activity of T-20 as a Single Agent in Heavily Pre-treated Patients
J. LALEZARI, J. ERON *, M. CARLSON, R. ARDUINO J. GOODGAME, C. COHEN, L. JONES, J. GLEAVY, A. DUSEK, T. VENETTA, E. DIMASSIMO, and S. HOPKINS for the TRI-003 STUDY GROUP Quest Clinical Research, San Francisco, CA; UNC-Chapel Hill, Chapel Hill, NC, UCLA, L.A., CA; UT-Houston, Houston, TX; Central Florida Research Initiative, Maitland, FL; CRINE, Brookline, MA; Trimeris Inc., Durham, NC

LB14 A Multi-Center, Randomized, Open-Label, Comparative Trial of the Clinical Benefit of Switching the ProteaseInhibitor (PI) by Nevirapine (NVP) in HAART-Experienced Patients Suffering Lipodystrophy (LD)
RUIZ L, BONJOCH A, PAREDES R, JOHNSTON S, ARNO A, ROMEU J, BALAGUE M, SIRERA G, TULDRA A, R. FUMAZ C, CLOTET B for the LD Study Group "irsiCaixa" Foundation. Hosp. Univ. Germans Trias i Pujol.Barcelona, Badalona, Spain.

LB16 [Late Breaker] A Phase III, Multicenter, Randomized, Open-Label Study to Compare the Antiretroviral Activity and Tolerability of Efavirenz (EFV) + Indinavir (IDV), versus EFV + Zidovudine (ZDV) + Lamivudine (3TC), versus IDV + ZDV + 3TC at 48 Weeks (Study DMP 266-006)
K. Tashima *, S. Staszewski, R. Stryker, P Johnson, M. Nelson, J. Morales-Ramirez, D.J. Manion, D. Farina, D. Labriola, N. Ruiz, and The Study 006 Investigator Team The Miriam Hospital, Providence, RI; Klinikum Der J.W. Goethe-Universtat, Frankfurt, German; Pacific Oaks Research, Beverly Hills, CA; UT Health Sciences Center, Houston, TX; St. Stevens Centre, London, UK; Doctor Diego Building, San Juan, PR; DuPont Pharmaceuticals Company, Wilmington, DE

LB3b [Late Breaker] Defect in Cytolytic Effector Molecules in Lymphoid Tissue (LT) during Primary HIV-1 Infection (PHI) is a Very Early Mechanism of Immune Dysfunction.
J. ANDERSSON*, P. RACZ, K. TENNER-RACZ, H-J STELLBRINK, S. KINLOCH, B. GAZZARD, M. TYRER, L. PERRIN, S. STASZEWSKI, M. BLOCH, D. COOPER, R. SEKALY AND L. GOH. For the QUEST Study Group. Stockholm, Sweden Hamburg, Germany London, UK Geneva Switzerland Frankfurt, Germany Sydney, Australia, Montreal, Canada Glaxo Wellcome, London, UK.

LB4 [Late Breaker] Sexual Transmission and Propagation of SIV and HIV-1 in Activated and Quiescent T Cells

Z.-Q. Zhang *, T. Schuler, S. Wietgrefe, K.A. Reimann, T.A. Reinhart, W. Cavert, C.J. Miller, R.S. Veazey, D. Notermans, S. Little, S.A. Danner, D.D. Richman, D. Havlir, J. Wong, N.L. Letvin, S. Wolinsky, A. T. Haase Univ. of Minnesota, Mpls, MN; Harvard Medical School, Boston, MA; Univ. of Pittsburgh, Pittsburgh, PA; UC-Davis, Davis, CA; Academic Medical Center, Amsterdam; UCSD, San Diego, CA; Northwestern Univ., Chicago, IL

LB5 [Late Breaker] Intermittent Drug Therapy Increases the Time to HIV Rebound in Humans and Induces the Control of SIV after Treatment Interruption in Monkeys.
F. LORI *, D. ZINN, G. VARGA, R. MASERATI E. SEMINARI, J. TIMPONE, N. MILLER, R. PAL, P. MARKHAM, J. LISZIEWICZ. Research Institute for Genetic and Human Therapy (RIGHT) Washington DC and Pavia IT; Policlinico S Matteo, Pavia IT; Georgetown Univ. Washington DC; NIAID, NIH, Bethesda MD; ABL, Kensington MD.

LB6 [Late Breaker] OKT3 and rhIL-2 in HIV-1 Patients on HAART with Prolonged Suppression of Plasma Viremia.
J PRINS*, S JURRIAANS, R van PRAAG, H BLAAK, P SCHELLEKENS, I ten BERGE, C FOX, M ROOS, F de WOLF, J GOUDSMIT, H SCHUITEMAKER, J LANGE. Univ. of Amsterdam, Amsterdam, the Netherlands; Molecular Histology, Gaithersburg, MD, USA.

LB7 Discontinuation of PCP prophylaxis (PRO) is safe in HIV-infected patients (PTS) with immunological recoverywith HAART. Preliminary results of an open, radomised and multicentric clinical trial (GESIDA04/98).
JC LOPEZ, JM PENA, JM MIRO, D PODZAMCZER, and the GESIDA 04/98 study group. Hosp. GregorioMaranon1 and La Paz2 (Madrid), Clinic3 and Bellvitge4 (Barcelona), Spain.
D.V. Havlir1*, R. Schrier1, F. Torriani, K. Chervenak, H. Boom, University of California, San Diego, CA1 and CaseWestern Reserve University, Cleveland, OH2.

LB8 [Late Breaker] A Pilot Study of the Short-Term Effects of Antiretroviral Management Based on Plasma Genotypic Antiretroviral Resistance Testing (GART) in Patients Failing Antiretroviral Therapy.
J.D. BAXTER*, D.L. MAYERS, D.N. WENTWORTH, J.D. NEATON, T.C. MERIGAN and the CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Cooper Hospital/UMC, Camden, NJ; Henry Ford Hospital, Detroit, MI; University of Minnesota, Minneapolis, MN; Stanford University, Stanford, CA.

LB9 [Late Breaker] High Frequency of Antiretroviral Drug Resistance in HIV-1 from Recently Infected Therapy Naive Individuals
S. Wegner*, J. Mascola, A. Barile, N. Aronson, G. Martin, K. Stephan, S. Brodine, S. Tasker, S. Bloor, J. Vingerhoets, K. Hertogs and B. Larder. U.S. Military HIV Research Program, Rockville, MD, Virco UK, Cambridge, U.K., Virco Belgium, Mechelen, Belgium

S11 Mechanism of CD4-Independent Infection
Robert Doms, Univ. of Pennsylvania, Philadelphia

S12 Proinflamatory Cytokines and Chemokines: Viral Strain Specific and Non-Specific Modulation of HIV-1 Replication.
A.Kinter*, M. Ruiz, E. Donoghue, A Catanzaro and A.S. Fauci

S13 The CC-Chemokine RANTES Has Multiple Effects on HIV-1 Replication in Primary and Transformed Cells
A. Trkola, C.J. Gordon, A. Garcia-Sastre, M.A. Muesing, L. Czaplewski, AEI Proudfoot, J.P. Moore, The Aaron Diamond AIDS Research Center, Department of Pathology, New York University School of Medicine, The Rockefeller University, Mount Sinai School of Medicine, British BiotechLtd., Oxford, UK, Serono Pharm., Research Inst., Geneva, Switz.

S13a Tyrosine Sulfation of the Amino-Terminus of CCR5 Facilitates HIV-1 Entry
M. Farzan, T. Mirzabekov, P. Kolchinsky, R. Wyatt, M. Cayabyab, N.P. Gerard, J. Sodroski, H. Choe, Children's Hosp., Harvard, Med., School, Boston, MA

S14 Pathogenesis: Disease Mechanisms in Humans and Animal Models the Human Genes That Limit AIDS
S. O'Brien, M. Dean, M. Carrington, C. Winkler, N. Smith, G. Nelson, and J.C. Stephens, Lab. of Genomic Diversity, NCI-FCRDC, Frederick, MD.

S2 The Origin of HIV-1: A Puzzle Solved?
F. Gao, E. Bailes, D. Robertson, Y. Chen, c. Rodenburg, S. Michael, L. Cummins, L. Arthur, M. Peeters. G. Shaw, P. Sharp, and B. Hahn.
Univ. of Alabama at Birmingham, Ala., Univ. of Nottingham, UK., CNRS, Marseille, France, Southwest Fndn. for Biomedical Research, San Antonio, Texas, FCRDC, Frederick MD., Lab. de Retrovirus, ORSTOM/SIDA, France, Howard Hughes Med. Inst., Univ. of Alabama, Birmingham, Ala.

S20 Abstract not submitted

S21 Mechanism of Nef-Dependent HIV-1, Infectivity Enhancement
A. Kotov, J. Zhou, and C. Aiken, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

S22 Analysis of Nef-induced MHC-1 Modulation

S. Le Gall, L. Erdtmann, S. Benichou, c. Berlioz-Torrent, L. Liu, R. Benarous, J.M. Heard, and O. Schwartz, Laboratoire Retrovirus et Transfert Genetique, Institut Pasteur and Institut Cochin de Genetique Moleculaire, Paris, France

S23 Indpendent Functions of Vpr Protein in Transcriptional Coactivation and Cell Cycle Arrest
George N. Pavlakis, Alexander Gragerov, Tomoshige Kino, Jeffrey B. Kopp, and George P. Chrousos, Human Retrovirus Section, ABL Res. Program, NCI-FCRDC, Frederick, MD., Section on Pediatric Endocrinology and Kidney Disease Section, NIH, Bethesda, MD.

S24 Abstract not submitted

S3 Disturbances in Lipid Metabolism due to HIV Infection and Its Therapy
C. Grunfeld, VA Medical Center and Univ. of California, San Francisco, CA.

S34 New Insights into Genetic Mechanisms of HIV Drug Resistance
B. Larder Virco, Cambridge, UK.

S37 NMR Studies of HIV-1 Genome Recognition and Retrovirus Assembly,
M.F. Summers, Howard Hughes Medical Inst. and Dept., of Chemistry and Biochemistry, Univ. of Maryland, Baltimore County, Baltimore, MD.

S38 Characterization of HIV-1 Matrix Function: Roles in Both Early and Late Steps of the Virus Life Cycle
Akira Ono, Rosemary E. Kiernan, and Eric O. Freed. NIAID, NIH, Bethesda, MD.

S40 Novel Functions of HIV-1 Matrix
H. Reil, J.C. Paillart, T. Dortman, and H.G. Gottlinger, Dana-Farber Cancer Inst., Boston, MA.

S41 Preserving HIV-1-specific T cell help: will it prevent progression?
Eric S. Roseberg, Barbara Wilkes, Sam Poon, Gregory Robbins, Paul Sax, Stephen Boswell, Mary Phillips, Benjamin Davis, Nesli Basgoz, Richard D'Aquila, and Bruce D. Walker, Mass. General Hospital and Harvard Medical School, Boston, MA.

S42 Thymic Contributions to Immune Reconstitution
D. Douek, R. McFarland, P. Keiser, J. Massey, B. Haynes, L. Picker, R. Koup, Dept. of Medicine and Pathology, The University of Texas Southwestern Medical Center, Dallas, Texas. Department of Medicine, Duke University Medical Center, Durham, North Carolina.

S43 T Cell Production in HIV-1 Disease
J.M. McCune, The Gladstone Inst. of Virology and Immunology, Univ. of California at San Francisco, San Francisco, CA.

S44 Effects of antiretroviral therapy on immune reconstitution
B. Autran, G. Carcelain, R. Tubiana, V. Calvez, A. Mallet, P. Debre, C. Katlama, Lab. Immunologie Cellulaire, Dept. Maladies Infectieuses, Lab. Virologie, Biomathmatiques INSERM U194, Hosp. Pitie-Salpetriere, Paris, France.

International AIDS Society–USA
Presidio of San Francisco
1001 B O'Reilly Avenue, Box 29916
San Francisco, CA 94129-0916

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