IMPROVING THE MANAGEMENT OF HIV DISEASE

IN THIS ISSUE

Highlights from the 5th Conference on Retroviruses and Opportunistic Infections, February 1-5, 1998

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ABOUT THIS ISSUE...

This issue of Improving the Management of HIV Disease is the first of several issues to be published in 1998. The issue contains a timely review of the new information that was presented at the 5th Conference on Retroviruses and Opportunistic Infections, held in Chicago in February. 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, including understandings in the functions of viral accessory genes, coreceptor interactions, and viral reservoirs. Dr Bruce Walker reviews new data regarding HIV pathogenesis, including correlates of protective immunity, reservoirs, and the impact of potent therapy on immune functions. 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 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 sixth annual series, Advanced CME Course in HIV Pathogenesis, Antiretrovirals, and Selected Issues in HIV Management. Courses in Boston (March 28), San Francisco (April 7), Chicago (April 22), New Orleans (May 2), and Cleveland (May 16) have been confirmed; please call the International AIDS Society-USA conference information line, 415-561-6725, for details.

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Basic Science

Mario Stevenson, PhD

Presentations in the basic science categories underscored the steady progress being made in understanding the functions of viral accessory genes. The identification of cellular intermediaries that interact with viral accessory gene products has revealed cellular pathways utilized by these proteins. This is beginning to provide insight into how these proteins may be important for virus replication. New findings on the interactions of primate lentiviruses with their coreceptors are promoting our understanding of how these interactions affect viral tropism, how the virus impacts on host cell physiology, and how levels of expression of coreceptor molecules impact on disease progression. Reservoirs of primate lentivirus infection, which may explain long-term latency/viral persistence in the face of antiretroviral therapy, were described by a number of investigators. The actual cells involved in maintaining long-term viral latency/persistence still remain an important but unresolved issue.

Accessory Genes

The accessory proteins arguably represent the most enigmatic of the primate lentivirus gene products. Several are unique to the primate lentiviruses and are conserved across primate lentivirus lineages. The accessory genes appear necessary for the pathogenicity of the virus, both in monkeys and in humans. Although a number of properties have been described for each of the accessory gene products, the actual role served by these proteins is not known for any of them. Ultimately, a greater understanding of these roles can be gained through the identification of cellular intermediates with which these accessory gene products interact and manifest their effect and it is in the identification of such cellular factors that the greatest progress is being made.

A well-recognized feature of virus infected CD4 cells in vitro is the rapid downregulation of the CD4 receptor (and also of coreceptor molecules). Three proteins, namely envelope, Nef, and Vpu, working at mechanistically different levels, have been shown to reduce the expression of CD4 on the cell surface. Vpu interacts with CD4 in the endoplasmic reticulum and targets CD4 for degradation likely in the proteasomes. A cellular protein that likely interacts with Vpu and directs Vpu/CD4 complexes for degradation was described (Abstract 25). A yeast genetic screen was used to identify cellular proteins that interact with Vpu. Using this approach, a protein has been identified (β-TRCP) that may be involved in Vpu-mediated targeting of CD4 to the degradation pathway. β-TRCP and Vpu were shown to interact in a yeast two-hybrid assay. The recombinant proteins could interact in vitro and could be co-immunoprecipitated when expressed in mammalian cells. Two serine residues shown previously to be necessary for downregulation of CD4 by Vpu were also important for interaction of Vpu with β-TRCP. Thus, it is likely that Vpu, CD4, and β-TRCP form a trimolecular complex where Vpu links CD4 to β-TRCP. Truncated mutants of β-TRCP prevented CD4 downregulation by Vpu. Further support for the role of β-TRCP in Vpu-mediated CD4 down-regulation was provided by the demonstration that β-TRCP interacts with a second cellular factor (Ski P1), a protein that targets the ubiquitin pathway. Therefore, following interaction of Vpu with CD4 in the endoplasmic reticulum, β-TRCP likely mediates interaction of the Vpu/CD4 complex with Ski P1 and, as a result, the complex is targeted for degradation in the proteasome. This elegant study provides a mechanism through which Vpu downregulates CD4. However, it is still not clear as to why downregulating its primary receptor is advantageous to the virus.

Research findings presented at the conference attempted to shed light on why CD4 downregulation is important for efficient virus replication. In addition to Vpu, CD4 receptor expression on the cell surface is also downregulated by the Nef accessory gene product. Nef protein appears to induce accelerated endocytosis of CD4. Thus, cells that express only HIV or SIV Nef proteins exhibit less CD4 on the cell surface. Studies by Trono (Abstract S40) indicate that Nef and Vpu counteract CD4-mediated inhibition of HIV infectivity. During virus exit from the producer cell, nascent envelope proteins need to be transported to the cell membrane for incorporation into assembling viral complexes. However, the interaction of nascent envelope glycoproteins with CD4 molecules poses a problem in that some envelope complexed to CD4 may be incorporated into viral particles. As a consequence, these virion-incorporated CD4 molecules may compete for available receptor binding sites on the target cell. In support of this notion, evidence was provided that overexpression of CD4 in producer cells markedly impaired HIV-1 infectivity. Virions released from such cells were shown to contain CD4 molecules. Nef and Vpu, by reducing surface CD4 expression in the producer cell, prevented virion
incorporation of CD4 and restored HIV infectivity. Overexpression of a CD4 mutant that did not bind envelope also did not impair viral infectivity. Similarly, overexpression of CD4 did not block infectivity of virus particles that contained a VSV-G envelope protein in place of HIV-1 envelope. Thus, by downregulating CD4, primate lentiviruses have evolved a mechanism that prevents receptor molecules in the producer cell from being incorporated into virions as complexes with envelope glycoproteins. Since such a process would be predicted to impair viral infectivity, the study by Trono may explain the functional significance of receptor downregulation by primate lentiviruses. It remains to be determined whether a similar problem is posed by interaction of envelope glycoproteins with coreceptor molecules and whether the virus has evolved a mechanism to prevent incorporation of coreceptor molecules into virions.

Several presentations addressed functions of the HIV-1 accessory gene product, Vpr. A number of properties have been described for this accessory gene product. Vpr facilitates nuclear translocation of the viral reverse transcription complex in non-dividing cells. Vpr, when expressed in cells, causes a delay in cell cycle progression. Vpr has also been shown to associate with the DNA repair enzyme, uracil DNA glycosylase, and, in addition, has been shown to function as a weak transcriptional activator of HIV-1 gene expression. A number of presenters focused on the nuclear import functions of Vpr. While Vpr has been demonstrated to localize to the nucleus and facilitate nuclear translocation of viral reverse transcription complexes, the protein contains no prototypic nuclear targeting signal that would support such a role. However, recent studies (Abstract 29) demonstrate that Vpr interacts with karyopherin-α which is involved in shuttling nuclear proteins to the nuclear pore complex. Vpr appears to act in a novel fashion. Normally, proteins containing a nuclear targeting signal interact with karyopherin and are subsequently targeted to the nuclear pore complex. Vpr appears to increase the affinity of proteins containing nuclear targeting signals for karyopherin, thus increasing the rate and extent of their nuclear transport. A second protein implicated in nuclear targeting of the viral reverse transcription complex is the structural gag MA protein. However, there have been several conflicting studies with regards to whether gag MA is a nuclear protein which promotes nuclear translocation of the viral reverse transcription complex. Vpr was shown to promote the interaction of gag MA with karyopherin. Vpr appears to act in a novel fashion in promoting nuclear targeting of viral proteins. Thus, it appears that Vpr strengthens the interaction of both weakly and strongly nucleophilic proteins for karyopherin. This study also provides a mechanistic explanation for why mutations in gag MA and Vpr result in an additive impairment in nuclear translocation of viral reverse transcription complexes in non-dividing cells.

Studies presented at the conference provided evidence that HIV-1 Vpr enters the cell nucleus by a novel nuclear transport pathway (Abstract 26). Two classical transport pathways have been implicated in directing nuclear proteins to the nuclear pore complex. These include the importin-α/ importin-β dependent and transportin-dependent pathways. The nuclear translocation of Vpr in this study was independent of either importin or transportin receptor pathways. In addition, through mutagenesis, two nuclear targeting motifs in Vpr were identified. Each of these nuclear localization signals function in a non-nuclear localization signal-dependent manner. Studies outlined by another group (Abstract 27) further addressed the role of Vpr nuclear localization in nuclear translocation of viral nucleic acids. The nuclear translocation of Vpr was dependent upon an intact α-helical domain and Vpr alleles with mutations in this domain (Q65E) localized to the cytoplasm. Surprisingly, different phenotypes were observed depending on the types of mutations introduced into Vpr. For example, some mutations in the α-helical domain prevented nuclear localization of Vpr and prevented provirus establishment in nondividing macrophages. Some mutations in Vpr did not affect nuclear translocation of the protein, yet markedly impaired virus replication in macrophages. Mutations that completely abrogated Vpr expression resulted in viruses that were able to integrate within macrophages, but which were unable to produce infectious virions. This phenotype has not been described previously for Vpr mutants and it will be important to confirm these results in order to identify how Vpr is influencing infectious virus production.

Studies from the laboratory of Emerman (Abstract S42) provided an update on studies into both nuclear import and cell cycle arrest properties of HIV-1 Vpr. Utilizing site specific mutagenesis, residues in Vpr that are important for its nuclear localization were identified. A Vpr F34I mutation caused a redistribution of this protein from the nucleus to the cytoplasm. This redistribution did not affect the ability of Vpr to delay cell cycle progression. However, this mutation introduced back into an infectious molecular clone markedly impaired the ability of the virus to infect nondividing macrophages without influencing its infection of T-cells. These data further substantiate the notion that the nuclear translocation of Vpr is important for the ability of the virus to infect nondividing cells. On the other hand, the role served by cell cycle
and infection of chimpanzees with HIV-1 represent non-pathogenic infections, this study suggests that viruses containing functional Vpr have a selective advantage even in such non-pathogenic infections. At present, however, it is unclear which of the Vpr functions (nuclear import, cell cycle arrest, uracil DNA glycosylase [UDG] association) was being selected for.

Additional effects of Vpr on host cell physiology were reported. Vpr was shown to induce T-cell receptor (TCR)-triggered apoptosis (Abstract 564). Thus, in the absence of TCR-mediated activation Vpr induced apoptosis, while in the presence of TCR-mediated activation Vpr interfered with the apoptotic pathway. This effect of Vpr on regulation of apoptosis was shown to be dependent on the suppression of NF-kB activity by Vpr. Independent studies (Abstract 565) demonstrated that HIV-1 Vpr induces gross morphologic changes within bone marrow cells cultured in vitro. Treatment of human marrow cells resulted in the promotion of adhesion of mononuclear phagocytes to culture plates with a concomitant increase in the association with nucleated and nonnucleated cells. This pattern is reminiscent of accelerated phagocytosis, which is itself indicative of monocye/macrophage activation. These studies suggest a role for Vpr in mononuclear phagocyte activation, which may promote productive viral infection or, through monocyte/macrophage activation, may provide a basis for the induction of cytopenias which are typical of HIV-1 infected individuals.

Studies provided further insight into the mechanism of action of Vif (viral infectivity factor) (Abstract 339). The vif gene is essential for virus replication within primary T-cells, macrophages, and certain cell lines, whereas some cell lines are permissive for productive infection by vif-minus viruses. Permissiveness cannot be restored when Vif is expressed in the target cell, suggesting that Vif modulates infectivity at a step late in the virus lifecycle, for example assembly, budding, or maturation. Although Vif has been shown to be contained within virus particles, reducing the amount of virion associated Vif by eightfold did not lead to a concomitant reduction in infectivity.

To determine how Vif influences viral infectivity, Malim et al examined the abilities of vif genes from divergent lentiviruses to complement each other. It was demonstrated that the Vif proteins of HIV-1 enhanced infectivity of SIVsm only in human cells. However, Vif proteins of SIVs from African green monkeys or Sykes monkeys were unable to influence infectivity of either HIV or SIV when expressed in human T-cells. Vif proteins of HIV also augmented the infectivity of the oncoretrovirus, murine leukemia virus (MLV) in human cells, even though MLV does not itself contain a recognized vif gene. Thus, Vif interacts with infected cells in a species-specific manner. The restricted nature of primate lentivirus/host cell interactions may be governed by the interaction between Vif and its cellular protein and this interaction itself may be species-specific.

Studies documenting the effects of the Nef (negative factor) accessory gene product on lymphocyte activation were presented (Abstract 341). Infection of interleukin-2 (IL-2)-dependent T-cell lines by SIVmac221 confers IL-2 independence. These infected cells release IL-2, suggesting that SIV augments IL-2 production in the infected host cell. The induction of IL-2 independence was found to be Nef-dependent. Intriguingly, HIV-1 Nef was found to functionally substitute for SIV-Nef in inducing IL-2 independence. These results raise the possibility that primate lentivirus Nef genes may influence lymphocyte acti-
vation via the IL-2/IL-2 receptor axis. Thus, virus-infected cells that are suboptimally activated may be brought to a higher level of activation through action of Nef on IL-2/IL-2 receptor-mediated activation, which would lead to a more permissive environment for virus replication in the host cell.

New data providing a mechanism for Nef-mediated CD4 downregulation were presented (Abstract S25). Nef-mediated CD4 downregulation was found to be dependent on CDC42/RAC1 and P21-activated kinase (PAK). A new Nef-binding protein (MBP1) was identified as the catalytic subunit of V-ATPase. Nef was shown to bind both MBP1 and CD4. The interaction of Nef with MBP1 resulted in the recruitment of Nef with bound CD4 to clathrin-coated pits, leading to rapid endocytosis of CD4 and subsequent degradation.

REGULATORY PROTEINS

Exciting new data providing further insight into the mechanism of action of regulatory proteins were presented at the conference. The Rev protein is essential for retrovirus replication. The interaction of Rev with a Rev-response element (RRE) in intron-containing RNAs results in their export from the nucleus. Studies of Weis (Abstract S24) have identified a new cellular protein that mediates Rev-dependent RNA export. Rev contains a nuclear export signal (NES) and a yeast protein known as exportin 1 was shown to interact with the NES of Rev and mediate its nuclear export. This finding opens the way for the development of new strategies to block the action of this essential viral gene product.

The Tat protein represents another essential viral regulatory gene product that regulates viral gene expression. Utilizing a biochemical screen, compounds that inhibit Tat-dependent transcriptional elongation have been identified (Abstract S27). These compounds were shown to inhibit PTEFb, a novel cellular kinase that influences transcriptional elongation of cellular genes. Mutant forms of PTEFb kinase were shown to block, in a transdominant fashion, Tat-dependent LTR transcription without influencing host cell physiology. Thus, these inhibitors are able to influence the action of PTEFb kinase on viral gene expression at concentrations, which leaves transcription of cellular genes unaffected. These agents represent potential novel therapeutics for the inhibition of HIV-1 replication.

STRUCTURAL PROTEINS

Previous studies documented the existence of tyrosine-based sorting signal on SIV-1 envelope glycoprotein that promoted rapid endocytosis of envelope via clathrin-coated pits. Thus, in infected cells, envelope glycoproteins have two fates: they are either incorporated into virus particles or they are rapidly endocytosed by clathrin-coated pits. The gag MA protein diverts HIV-1 envelope away from the endocytosis pathway. It has been suggested that this mechanism ensures that only those envelope glycoproteins that are competent for virion incorporation (which are MA associated) are target ed to the membrane. New studies presented at the conference (Abstract S20) investigated the in vivo significance of tyrosine-based sorting signals on lentiviral envelope glycoproteins. A highly conserved tyrosine (amino acid 721) in gp41 of SIV MAC239 that forms part of a sorting signal, was mutated, and in vitro and in vivo properties of viruses containing substitutions at this residue were examined. Replication of a gp41 Y721 mutant in macaque peripheral blood mononuclear cells (PBMCs) or in CEM X174 T-cells was unaffected, and there was no reversion of the mutation during multiple passages in culture. In contrast, the gp41 Y721 mutant exhibited an impaired phenotype in rhesus macaques. In one infected animal, reversion of the mutation back to wild-type sequence within three months of infection was observed. In one animal that showed no reversion, there was an approximately 2 log reduction in peak virus load. These studies provide evidence that tyrosine-based sorting signals in the gp41 portion of the envelope glycoprotein are important for in vivo virus replication and pathogenicity.

VIRUS-HOST CELL INTERACTIONS AND VIRAL CORECEPTORS

Previously published studies have suggested that polymorphisms (V64I) in the CCR2 gene delay disease progression. These results were subsequently challenged by a report demonstrating no effect of CCR2 polymorphisms on disease progression. Studies presented by Doms (Abstract S6) addressed this issue. In vitro experiments demonstrated that CCR2b containing a V64I mutation supported viral fusion and infection as efficiently as did wild-type virus. Expression of CCR2b did not affect expression of other coreceptor molecules in trans. However, both wild-type and V64I versions of CCR2b were able to desensitize the major HIV-1 coreceptors. Collectively, however, the studies failed to show a direct effect of the CCR2b V64I polymorphism on receptor function and virus infection.

In contrast, data on CCR2b genotypes in 954 DNA samples from infected and uninfected patients in the Chicago Multicenter AIDS Cohort Study (MACS) cohort were presented by Moore (Abstract S3), which may clarify the debate on the role of CCR2b polymorphisms on disease progression. Data were presented that the CCR2 64I allele was associated
with increased survival and reduced rate of CD4+ cell depletion, but only in a sero-incident and not in a sero-converter cohort. The V64I mutation in the CCR2b allele was found to have a genetic association with polymorphisms in the CCR5 regulatory region. These polymorphisms in the CCR5 promoter likely reduce the level of CCR5 expression and subsequently impair virus replication and disease progression. In further studies, 8 different substitutions in the CCR5 promoter were identified (for example, 353C, 402A). These promoter polymorphisms had a protective effect on disease progression in the context of individuals with a heterozygous CCR5Δ32 genotype or a CCR2b 64I genotype. In some cases, these polymorphisms were correlated with a reduced binding of MIP1-β by CCR5. Thus, the combination of CCR5 promoter polymorphisms with either CCR2b 64I or heterozygous Δ32 CCR5 mutations results in delayed disease progression. Why this is apparent in sero-incident and not in sero-converter cohorts is unknown.

Studies examining the correlation between the syncytium-inducing (SI) phenotype of primary isolates and their tropism were presented (Abstract S4). Several studies demonstrated previously that SI HIV-1 strains usually emerge late in disease and are associated with a more rapid decline in CD4+ T-cell counts. The SI phenotype is the result of adaptation to the use of CXCR4 coreceptor usage in vitro. A panel of primary isolates was examined for the ability to infect macrophages from normal donors and from individuals with a homozygous Δ32 CCR5 deletion. Some of these viruses (for example, HIV-1Δ32Δ64) were able to infect macrophages from normal and from Δ32 CCR5 homozygous individuals with equal efficiency. The infection of macrophages by HIV-1Δ32Δ64 was not inhibited by AOP RANTES (which blocks CCR5 coreceptor usage) but was inhibited by SDF-1, suggesting that some viruses are able to use CXCR4 for entry into primary macrophages. Variations on this theme were also noticed in that some viruses could use either CCR5 or CXCR4 for macrophage infection.

The in vivo pattern of coreceptor expression was presented (Abstract 276). In both lymphoid and non-lymphoid tissues, CD4+ T-cells and macrophages were found to be the major cell populations expressing CXCR4, CCR3, and CCR5. High-level CXCR4, CCR3 and CCR5 expression were observed in T-cells and macrophages at various anatomic sites. However, the expression is limited to a small fraction of these cells. Surprisingly, S100 dendritic cells did not appear to express significant levels of coreceptor molecules. Macrophages in the colon were found to express high levels of CXCR4 and CCR3. Significant levels of coreceptor expression were observed in the cells in the cervix but not in the vagina. Brain neurons were found to be highly positive for CXCR4 and CCR3 molecules, but surprisingly, no CCR5 expression was observed in these cells. Studies examining the expression of coreceptor molecules on CD34+ stem cells were examined (Abstract 275). CD34+ stem cells obtained from umbilical cord blood were found to express low to undetectable levels of CD4 and CCR5. Upon differentiation in culture, CD34 expression decreased while there was a concomitant increase in CD4 and CCR5 expression. As expected, these cells were permissive to HIV infection only after differentiation and upregulation of primary and coreceptor molecules. Upon differentiation in culture, these cells were only infectible by macrophage tropic HIV and not by T-cell tropic viruses, suggesting that CXCR4 is either present at suboptimal levels or cannot be utilized for infection of these cells.

Primary peripheral blood monocytes are refractory to HIV-1 infection. Upon differentiation to macrophages in vitro, cells become fully permissive to virus infection. This increased permissiveness to virus infection upon differentiation was shown to correlate with levels of CCR5 expression (Abstract 40). Surface expression of CCR5 and levels of CCR5 mRNA were increased upon monocyte differentiation. Furthermore, studies from another group (Abstract 39) presented evidence that HIV-1 infection of macrophages promotes CCR5 expression. FACS analysis demonstrated that CCR5 was expressed on a subpopulation of uninfected peripheral blood monocyte-derived macrophages. Following HIV-1 infection, however, a significant expansion of CCR5+ cells was observed and this was directly reflected by increases in the level of CCR5 mRNA expression. Thus, HIV-1 is able to augment CCR5 expression and thus, promote conditions for further virus spread and replication.

Several groups have turned their attention to establishing small animal models of primate lentivirus infection. In addition to receptor restrictions, the poor activity of regulatory genes in mouse cells has precluded the use of the mouse as a small animal model for primate lentivirus infection. However, expression of CCR5 and human CD4 in rabbit epithelial cells was shown to increase their permissiveness to HIV-1 infection (Abstract 43). These cells were infectible by CCR5-dependent HIV-1 strains but were not infectible by CXCR4-dependent strains. These studies raise the possibility that transgenic rabbits expressing human CCR5 and CD4 may provide a permissive small animal model for primate lentivirus infection. Studies presented at the conference suggested that CXCR4 usage is a fundamental feature of lentivirus biology (Abstract 44). Thus, infectivity and
HIGHLIGHTS OF THE 5TH RETROVIRUS CONFERENCE

SYNCYTIUM-INDUCING CAPACITY OF FIV IN HUMAN CELLS WAS FOUND TO BE CXCR4 DEPENDENT AND CD4 INDEPENDENT. THIS, CXCR4 USAGE APPEARS TO BE EXHIBITED BY DISTANTLY RELATED LENTIVIRUSES THAT CAUSE AN AIDS-LIKE DISEASE.

INFECTION OF CELLS BY HIV AND SIV IN VITRO LEADS TO THE ONSET OF VIRAL CYTOPATHIC EFFECTS. THE MECHANISMS THROUGH WHICH PRIMATE LENTIVIRUSES INDUCE HOST CELL CYTOLYSIS ARE POORLY UNDERSTOOD, BUT HAVE PREVIOUSLY BEEN SHOWN TO BE ENVELOPE-DEPENDENT. STORIES FROM THE BALTIMORE LABORATORY (ABSTRACT 285) ATTEMPTED TO EXAMINE THE ROLE OF APOPTOSIS IN VIRUS-MEDIATED CYTOPATHICITY. HIV-1 WAS SHOWN TO DIRECT CELL KILLING OF INFECTED T-CELLS RATHER THAN INDIRECT KILLING OF UNINFECTED CELLS AND THAT THIS KILLING APPEARED TO INVOLVE APOPTOSIS. IN ADDITION, VIRUSES WITH TROPIC ENVELOPES EXHIBITED GREATER CYTOPATHIC PROPERTIES THAN VIRUSES CONTAINING MACROPHAGE TROPIC ENVELOPES. HIV-1 INFECTION OF T-CELLS WAS ALSO OBSERVED IN PRIMARY LYMPHOCYTES FROM PATIENTS WHO HAD A GENETICALLY DEFECTIVE FAS PATHWAY, SUGGESTING HIV-1 IS KILLING T-CELLS BY FAS-INDEPENDENT MECHANISM. THESE STUDIES CHALLENGE EARLIER STUDIES IMPLICATING FAS IN HIV-1 INDUCED CYTOLYSIS.

VIRAL RESERVOIRS

AN EXAMINATION OF VIRAL CLEARANCE RATES FOLLOWING INITIATION OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY HAS DEMONSTRATED RAPID AND SLOW PHASES OF VIRAL CLEARANCE. A NUMBER OF INVESTIGATORS HAVE BEEN CHARACTERIZING VIRAL RESERVOIRS AND THE HALF-LIFE OF VIRUSES WITHIN THESE RESERVOIRS IN ORDER TO DETERMINE THE BASIS FOR THESE DIFFERENT CLEARANCE RATES. TO DATE, MOST OF THE INFORMATION AVAILABLE ON VIRUS TURNOVER HAS BEEN GAINED FROM AN EXAMINATION OF THE DECAY CURVES OF PLASMA VIRIONS FOLLOWING INITIATION OF POTENT ANTIRETROVIRAL THERAPY. THE INITIAL DECAY PHASE INDUCED BY ANTIRETROVIRAL THERAPY OCCURS OVER THE FIRST TWO WEEKS AND LEADS TO A 1- TO 2-LOG DROP IN PLASMA VIRUS LEVELS. IT HAS BEEN PROPOSED THAT THIS INITIAL RAPID DECAY PHASE REFLECTS THE RAPID CLEARANCE OF PRODUCTIVELY INFECTED T-LYMPHOCYTES. THIS, AN EXTREMELY IMPORTANT BUT UNADDRESSED ISSUE REGARDS THE NATURE OF THE VIRAL RESERVOIR THAT RESPONDS LESS EFFECTIVELY TO ANTIRETROVIRAL THERAPY DURING THE SECOND DECAY PHASE. HUAN (ABSTRACT S16) EXAMINED CHANGES IN PBMC-ASSOCIATED VIRAL DNA OVER TIME IN 18 INDIVIDUALS WHO HAD NO DETECTABLE PLASMA VIRIONS. PROVIRAL DNA HALF-LIVES OF BETWEEN 83 AND 124 DAYS WERE OBSERVED. IN AGREEMENT WITH THESE CALCULATIONS, A HALF-LIFE OF BETWEEN 104 AND 108 DAYS WAS OBSERVED FOR PBMC-ASSOCIATED PROVI RAL DNA IN INDIVIDUALS UNDERGOING POTENT ANTIRETROVIRAL THERAPY (ABSTRACT 515). THIS STUDY ALSO DEMONSTRATED THAT THERE WAS AN APPROXIMATELY 20-FOLD HIGHER LEVEL OF UNINTEGRATED VIRAL DNA THAN INTEGRATED SEQUENCES IN PBMCs OF INDIVIDUALS WHO HAD BARELY DETECTABLE LEVELS OF PLASMA VIRIONS. IN THE RETROVIRUS LIFECYCLE, UNINTEGRATED VIRAL DNA HAS A RELATIVELY SHORT HALF-LIFE (ON THE ORDER OF 1 TO 7 DAYS IN VITRO), WHEREAS INTEGRATED OR PROVIRAL DNA IS MAINTAINED FOR THE LIFE OF THE CELL. THE PRESENCE OF UNINTEGRATED VIRAL DNA INDICATES THAT THESE CELLS WERE INFECTED LATELY. THIS, THEREFORE, DOCUMENTS CONTINUED REPLICATION IN INDIVIDUALS UNDERGOING POTENT ANTIRETROVIRAL THERAPY DESPITE UNDECTECTABLE LEVELS OF PLASMA VIRIONS. IT RAISES QUESTIONS AS TO THE POSSIBLE EXISTENCE OF SANCTUARY SITES IN WHICH CELLS (MACROPHAGES, DENDRITIC CELLS, PERIODICALLY INFECTED T-CELLS) CAN MAINTAIN VIRUS PRODUCTION USING THE SUBSTRATE OF INFECTED T-CELLS. IN THE FACE OF POTENT ANTIRETROVIRAL THERAPY, AN ANALYSIS OF THE FREQUENCY OF VIRUS-INFECTED MACROPHAGES AND T-CELLS IN EARLY AND LATE STAGES OF INFECT (ABSTRACT S17) ALSO SUPPORTED THE NOTION THAT THE MAJOR SOURCE OF HIV IN TISSUES FOLLOWING POTENT ANTIRETROVIRAL THERAPY ARE SMALL NUMBERS OF PRODUC TIVELY INFECTED CELLS RATHER THAN REACTIVATION OF LATENTLY INFECTED CELLS. STUDIES BY BUCY AND COLLEAGUES DEMONSTRATED THAT FOLLOWING ANTIRETROVIRAL THERAPY, THE RELATIVE VIRAL RN A COPY NUMBER IN EACH INFECTED CELL DID NOT CHANGE SIGNIFICANTLY. ONLY THE FREQUENCY OF INFECTED CELLS SHOWED A SIGNIFICANT CHANGE. FURTHERMORE, THE FREQUENCY OF INFECTED CELLS DID NOT CORRELATE WITH THE NUMBER OF PLASMA VIRIONS. THESE DATA ARE MORE CONSISTENT WITH THE MAINTENANCE OF A SMALL POPULATION OF PRODUCTIVELY INFECTED CELLS RATHER THAN REACTIVATION OF AN EXISTING LATENT RESERVOIR. IT WAS ALSO EMphasized THAT DUE TO THE RAPID CLEARANCE OF VIRUS IN THE IMMUNE SYSTEM BY FOLLCULAR DENDRITIC CELLS, THE AMOUNT OF VIRUS PRODUCED IN THE HOST IS NOT RELIABLY REPRESENTED BY THE AMOUNT OF VIRUS THAT CAN BE MEASURED IN PLASMA.

AN EXAMINATION OF THE VIRAL CLEARANCE RATES IN MONKEYS PROVIDED INDICES THAT WERE SIMILAR TO THOSE MEASURED FOR HIV-1 INFECTION IN INFECTED HUMANS. STUDIES OUTLINED BY FEINBERG AND COLLEAGUES (ABSTRACT 274) DOCUMENTED VIRAL CLEARANCE RATES IN NATURALLY-INFECTED SOOTY MANGABEYS. SUCH NATURALLY-INFECTED MONKEYS SHOWED NO EVIDENCE OF DISEASE DESPITE HIGH VIRUS LOADS. FOLLOWING INHIBITION OF VIRUS REPLICATION WITH PMPA, TWO VIRAL DECAY PHASES WERE OBSERVED. THE FIRST WAS CHARACTERIZED BY A HALF-LIFE OF 0.66 TO 1.15 DAYS AND THE SECOND, SLOWER HALF-LIFE OF 5.9 TO 20 DAYS. REMARKABLY, THESE DECAY RATES ARE SIMILAR TO WHAT HAS BEEN REPORTED IN PATHOGENIC (HIV-1 INFECTION OF HUMANS) INFECTIONS. THEREFORE, VIRAL TURNOVER RATES APPEAR TO BE SIMILAR IN PATHOGENIC AND NONPATHOGENIC PRIMATE LENTIVIRUS INFECTIONS. HO AND COLLEAGUES (ABSTRACT 272) EXAMINED LYMPHOCYTE TURNOVER DYNAMICS IN SIV-INFECTED RHESUS MONKEYS. A DEBATED ISSUE IS WHETHER THE INCREASE IN NUMBER OF CIRCULATING CD4
lymphocytes following inhibition of virus replication with antiretrovirals represents protection of cells from virus-mediated killing or whether it is a consequence of lymphocytes redistributing between tissue compartments. Using in vivo labeling of cycling cells with bromodeoxyuridine, the Ho group provided solid evidence for T cell turnover in the face of SIV infection.

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HIV PATHOGENESIS

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New findings related to HIV pathogenesis were largely extensions of the dramatic advances made during the past year. This review will focus on several key areas that are of particular relevance in terms of clinical interventions. These include new advances in our understanding of the correlates of protective immunity, new insights into the persistence of tissue reservoirs of virus, and the impact of potent antiretroviral therapy on immune function in HIV-1-infected persons.

CORRELATES OF IMMUNE PROTECTION IN HIV-1 INFECTION

One of the central unresolved issues related to disease pathogenesis is the identification of protective immune responses in HIV-1 infection. Letvin (Abstract L3) presented data from acute infection of rhesus macaques with a pathogenic simian immunodeficiency virus (SIV) isolate, providing new insights into the dynamics of the early cellular immune response. By day six after experimental infection, approximately 5% to 10% of all T cells in the regional lymph nodes are replicating virus, and by day 16 this robust replication has already been significantly contained. An oligoclonal cytotoxic T-lymphocyte (CTL) response can be detected in the regional lymph nodes within 72 hours of mucosal exposure, indicating that this arm of the immune response is induced very early after infection. This is long before neutralizing antibodies are detected, providing further evidence that CTLs are assisting in containing replication. Additional animal model studies in reconstituted severe-combined immunodeficiency disease (SCID) mice also supported an important role for CTL, in that CD8+ cells mediate resistance to HIV infection (Abstract 90), and that passive transfer of antibody does not modulate disease progression in these mice after experimental infection (Abstract 101).

Strong immune responses to HIV thus appear to be important in containing the virus, and emerging data raise the important question as to whether genetic polymorphisms may in fact modulate the specific immune responses generated in response to HIV-1 infection (Symposium 9). There now seems to be consensus that the V62I mutation in the chemokine receptor CCR2 is associated with a decreased rate of disease progression only in seroconverting cohorts, and not in studies of seroconverters (Abstract S3, S45a). This is likely due to the slight effect that is conferred, such that it can only be observed when cohorts are closely matched for time of infection. Moore presented an important new genetic analysis that may help to explain the observation that a CCR2 polymorphism is associated with reduced disease progression in seroconverters. This has been a curious finding because CCR2 is not a major co-receptor for viral entry. Moore described a genetic polymorphism in the CCR5 promoter region, which is 100% linked with the V62I mutation in CCR2 as shown by a novel molecular beacon technology (Abstract S3). This particular mutation in the promoter region may affect CCR5 expression, thus accounting for its observed effects on disease progression. These data provide further support for the development of therapies designed to block viral entry via the chemokine receptors.

Studies of persons at opposite ends of the progression spectrum are now beginning to shed light on the role of virus-specific immune responses in disease progression. In a plenary session, it was reported that virus-specific helper cell responses directed at the viral p24 protein are associated with the control of viremia in long-term non-progressors who have not been treated with antiviral therapy (Abstract L4). This finding was confirmed by Autran (personal communication) with data generated from a cohort of non-progressing persons in Paris, France. New data presented at the Conference suggest that these helper cells mediate their antiviral activity through the modulation of virus-specific CTLs, since strong helper cell responses are always associated with strong CTL responses (Abstract L4). This finding is consistent with the detailed characterization of a person with rapidly progressive infection, in whom strong CTL responses were detected just after seroconversion but they rapidly waned (Abstract 73). CTLs could be detected up until the time of this patient’s death, which were able to recognize endogenous viruses present, indicating that emergence of immune escape was not playing an important role in disease progression. However, these CTLs did not expand in vivo, and the CTL response did not diversify over time. These data suggest the presence of an activation block in vivo. Analysis of virus-specific helper cell responses in this person revealed a dramatic lack of detectable responses, providing a potential explanation for the lack of in vivo activation. Another potential explanation is the report that circulating CD8+ lymphocytes downmodulate the CD3 zeta chain (Abstract 105). Since the zeta chain expression is increased following exposure to inter-
leukin-2 (IL-2), it is possible that a deficiency of this cytokine contributes to impaired CTL function in vivo.

In addition to specific immune dysfunction leading to disease progression, it is also possible that viral attenuation may contribute to differences in disease course. One possible mutation affecting the pathogenicity of HIV was reported in the SIV model by Hoxie (Abstract 520). All SIV and HIV isolates reported to date contain a highly conserved tyrosine in the cytoplasmic tail of the transmembrane protein gp41 at position 721, which is part of an endocytosis signal for membrane glycoproteins. Substitution of the Tyr by Ile or deletion of the Tyr resulted in markedly attenuated disease and lower viral load in macaques experimentally infected with SIV. Whether the attenuated pathogenicity is due to an immune response is currently under investigation.

PERSISTENCE OF VIRAL RESERVOIRS DURING THERAPY

One of the most important advances in understanding HIV-1 pathogenesis and the possibility of virus eradication was the identification in 1997 of persistent viral reservoirs. A number of studies presented at the conference confirm and extend these findings. Siliciano, who was the first to report on these reservoirs of post-integration latency, presented extended data on persons who received potent antiretroviral therapy for periods of up to 30 months (Abstract S15a). Eighteen of 22 persons evaluated had detectable infectious virus that was isolated from resting CD4+ lymphocytes; in the other 4 individuals there were insufficient cells isolated to complete the study. Of note, some of the isolated viruses were syncytium-inducing phenotypes. Importantly, the size of the latent reservoir was found to be of the same order of magnitude for persons treated for 2 years with potent antiretroviral therapy, persons treated for just 2 months, and persons who did not receive therapy. In preliminary longitudinal studies there was no evidence of a progressive decay in the size of the reservoir, indicating that it has some intrinsic stability.

Other investigators also examined the residual reservoir during potent antiretroviral therapy. Wong presented data showing viral transcriptional activity in CD4+ cells despite prolonged antiretroviral therapy, and persistence of recoverable infectious virus (Abstract S19). Ho (Abstract S16) reported that the isolation rate for infectious virus decreased from 43% at 18 months to 28% at 22 months. Although this difference was not statistically significant, aggregate data suggested a progressive decline in the size of the cellular reservoir. He also examined proviral DNA and preliminary evaluation suggested a steady decay with a half-life of 110 to 120 days. He also reported that multiply-spliced RNA was not detected, only unspliced RNA was, which he speculated could be produced by defective viruses or be due to trapped virions. The residual pool after 15 months of effective therapy was calculated to be a mean of 30,000 cells (range 4000-100,000 cells), and thus Ho’s estimate of pool size is approximately tenfold lower than that reported by Siliciano. There was much variability in the decay rate calculation, but at best this seemed to be a half-life of 3 months. If one assumes the worst-case scenario, with a pool size of 100,000 and a decay rate of 18 months, then it would take more than 20 years to reduce the body burden to less than one infected cell.

An assessment of the cellular location of the persistent virus infection was provided by Bucy (Abstract S17). In situ studies revealed that 85% to 100% of the residual pool of RNA-positive cells are T cells, a finding supported by Shacker (Abstract 523). This remains the case even after prolonged potent antiretroviral therapy: although this led to an increase in the relative percentage of macrophages in lymph nodes, the cells harboring viral RNA were still predominately T cells. In a separate session, Bucy posited that much of the increase in CD4+ cell number seen early after potent antiretroviral therapy may be due to redistribution (Abstract 519). He suggested that immune activation was leading to increased sequestration of virus in lymph nodes. He presented data from lymph nodes obtained from ACTG 328 in which persons were treated with potent antiretroviral therapy. The total number of cells in lymph nodes was found to decrease with treatment, and staining with antibodies to adhesion molecules markedly decreased. This was interpreted to be consistent with a decrease in lymph node sequestration due to a decrease in adhesion markers on CD4+ cells, which in turn was due to decreased antigen exposure following institution of therapy. Further studies seem warranted to address this issue. One such study by Helfenstein (Abstract 273) suggests that increases in T-cells following institution of therapy may be due to increased rates of T-cell proliferation.

EFFECTS OF ANTIRETROVIRAL THERAPY ON IMMUNE FUNCTION

A major issue related to antiretroviral therapy is whether this therapy alone will lead to enhanced virus-specific immune responses. At last year’s Conference there was considerable excitement due to data presented by Autran, since published in Science, that potent antiretroviral therapy led to an increase in naive CD4+ cells. This offered hope that infected persons might generate enhanced immunity to HIV-1 following prolonged therapy, but numerous studies indicate that this
is not the case, at least over the 1 to 2 years of follow-up thus far. One possibility is that persons have just not been treated long enough to expect immune reconstitution, particularly given the slow kinetics of immune reconstitution following intensive chemotherapy (Abstract 1.7).

Prolonged therapy with potent antiretroviral therapy has been associated with some measurable changes in immune function. CD4+ and CD8+ cell numbers increase rapidly in the first few weeks of therapy, with T-cell receptor analysis suggesting early redistribution followed by de novo repopulating with naïve cells (Abstract 20). In terms of the virus-specific immune responses, different groups reported that prolonged therapy resulted in diminished CTL responses as might be expected with the decrease in antigen to drive this response (Abstracts 19, 522).

However, potent antiretroviral therapy in the earliest stages of infection does clearly result in the generation of vigorous virus-specific CD4+ helper cell responses directed at the viral p24 protein. It was reported at the conference that 11 of 11 persons who were treated in the pre-seroconversion stage of infection all developed vigorous p24-specific helper cell responses, and a portion of these persons also developed gp160-specific responses (Abstract 5.4). These responses were persistent at up to one year of follow-up, despite the fact that viral loads had been persistently below the limits of detection by sensitive RNA assays. The magnitude and breadth of these responses were reported to be analogous to those seen in persons in whom viremia is controlled in the absence of antiretroviral therapy. However, these persons treated in the earliest stages of infection were reported to still have abnormal CD4+ and CD8 profiles, such as decreased IL-2 receptor expression, which persisted with therapy (Abstract 587).

The above studies of early intervention raise the question as to whether persons treated in the earliest stages of infection develop a mature immune response that is able to control the virus. There was one report at the conference that suggests this may be the case. Lori reported on a cohort of patients treated by Jessen in Berlin, who were given a combination of didanosine, hydroxyurea and a protease inhibition prior to seroconversion (Abstract LB11). All of these persons developed undetectable viral loads on therapy, and remain well at a year or more of follow-up. One individual stopped therapy after 6 months and maintains a viral load below the limits of detection one year later. Replication competent virus could be recovered from his resting CD4+ cells, at levels comparable to those seen in other treated persons, but he has not become viremic (Abstract S15a). Whether this person is maintaining an undetectable load due to immune control is a vital question that needs to be answered. This report also has to be viewed in the context of another report that a person treated during the acute retroviral syndrome developed a recurrent symptomatic retroviral syndrome after stopping therapy at six months (Abstract 588).

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NEW INSIGHTS INTO HIV-RELATED COMPLICATIONS

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Epidemiology

A consistent theme at this year’s conference was the continued decline in rates of opportunistic infections (OIs) and AIDS-related deaths in the developed world. In a plenary session, DeCock from the Centers for Disease Control and Prevention (CDC) reported a 44% decline in the rate of AIDS deaths and a 12% decline in new AIDS cases for the first half of 1997, compared with 1996 (Abstract L2). DeCock discussed strategies for improving prevention efforts and identified improved treatment of sexually transmitted disease (STD) treatment and educational efforts targeted at HIV-infected individuals as priorities.

Evidence for improved treatment outcome was reported by several groups of investigators. Chiasson and colleagues from the New York City Department of Health reported a 33% decline in AIDS deaths for the first half of 1997, compared with 1996. This rate of decline was even greater than that observed in 1996 (Abstract 9B). The number of deaths declined for both men and women, and the greatest change compared to the prior year was seen among black women. In this subgroup, there was a 30% decline in deaths compared with a 16% decline in the previous year. A population-based, case control study of AIDS-related deaths in New York conducted by Reggy et al. identified the use of protease inhibitors as an important factor in reducing the rate of death (Abstract LB7). Researchers from the CDC-funded Adult Spectrum of Disease Project examined predictors of survival among more than 8000 adults receiving HIV care at United States sites, and identified the use of combination antiretroviral therapy, and prophylaxis of Pneumocystis carinii pneumonia (PCP) and Mycobacterium avium complex (MAC), as contributing factors (Abstract 10).

Spectrum and Risks for Opportunistic Infections

As rates of OIs have declined there has been interest in the spectrum and presentation of specific diseases. At this year’s conference, data were presented by several groups on the magnitude of the decline in rates of OIs. The French Clinical Epidemiology Database represents one of the most comprehensive sources of data on the rates of OIs (Abstract 182). Costagliola and colleagues from this group reported the declines in specific OIs, comparing the first semesters of 1996 and 1997 among nearly 60,000 HIV-infected adults enrolled in a prospective cohort study. Declines were seen in all types of AIDS-related conditions, but the greatest declines were observed in diseases that occur in patients with the most advanced disease.

Cytomegalovirus (CMV) disease was reduced by 80%, MAC by 73%, cryptococcosis by 70%, and esophageal candidiasis by 69%. Interestingly, bacterial pneumonia (1.7 cases per 100-patient-years) emerged as the most common complication observed during the first half of 1997 followed by esophageal candidiasis (1.0 case per 100-patient-years). Canadian investigators reported on trends in AIDS diagnoses between 1994 and 1996 and observed a decline in new AIDS diagnoses, but no change in the relative frequency of different infections and no change in the CD4+ cell count at which OIs occurred (Abstract 179). Several groups of US investigators (Abstracts 180, 183, 184) reported similar findings with declines in the rates of all OIs and a consistent finding of dramatic declines in CMV and MAC infections. Huang and colleagues reviewed the records of patients who developed PCP in San Francisco and noted the decline in PCP rates and identified that new PCP cases were occurring in patients who were either not on prophylaxis or non-adherent to therapy (Abstract 185).

Defining the relationship between routine laboratory markers such as viral load or CD4+ cell counts and the risk for OIs remains an area of active investigation. Investigators from the Multicenter AIDS Cohort Study examined risk factors for CMV, MAC, and PCP during the pre-therapy era and found that plasma viral load, CD4+ cell count, and prior AIDS diagnoses were all important factors but contributed differently to the risk of each infection. Data from ACTG 320, a trial comparing combination nucleoside analogue reverse transcriptase inhibitor (nRTI) therapy with a triple combination of zidovudine/lamivudine/indinavir, identified PCP, CMV, and MAC as the most common OIs occurring after the initiation of protease inhibitor therapy (Abstract 257). In this study, the OIs that occurred in the three-drug arm tended to occur early. Higher pretreatment plasma HIV RNA values, and failure of CD4+ cell count to increase or of HIV RNA level to decrease identified patients at continued risk to developing an infection. In other words, the patients who developed OIs on the three-drug arm were those
who were not responding to therapy. Data from the Hopkins cohort presented by Moore also reported no OIs occurring in patients on therapy with CD4+ cell counts greater than 200 cells/μL, supporting the notion that therapy-induced CD4+ cell count increases provide protection against clinical progression (Abstract 184).

A new area of investigation highlighted at this year’s conference was the metabolic complications of HIV disease and HIV therapy. Abnormal accumulations of fat, both in the neck and shoulder region (“buffalo hump”) and in the abdomen were described in small numbers of patients receiving protease inhibitor therapy by seven different groups (Abstracts 407-413). A common theme in these reports was a finding of normal cortisol levels and a range of abnormal triglyceride responses. One group identified this syndrome in a few patients who were not on protease inhibitor therapy (Abstract 409), while the others all focused on the syndrome in patients receiving protease inhibitors. A novel hypothesis put forth by Carr and colleagues suggested that sequence homology between the 12 amino acids spanning the catalytic site of the HIV protease and low density lipoprotein receptor-like protein might explain the interaction between protease inhibitor therapy and lipodystrophy. Clearly, further work is needed to define the cause of these abnormal fat depositions. Further data on hyperglycemia during protease inhibitor therapy were also reported. Keruly et al reported an incidence rate of 0.35 cases of severe hyperglycemia per 100 person months of protease inhibitor, and 0.52 cases of any degree of hyperglycemia during protease inhibitor therapy from the Hopkins cohort (Abstract 415). Six additional cases of hyperglycemia associated with protease inhibitor therapy were reported, and highlighted the fact any protease inhibitor can produce this effect, but the frequency of this metabolic abnormality is relatively rare (Abstract 416).

**Clinical Presentation and Outcome of Opportunistic Infections**

A more complete picture of the outcome of established OIs after the initiation of potent combination therapy is emerging. In a prospective follow-up of patients with CMV retinitis from San Diego, Freeman and colleagues noted a delay in time to CMV reactivation in individuals receiving potent antiretroviral therapy who had discontinued CMV maintenance therapy (Abstract 757). Specifically, 7 of 8 patients who discontinued CMV therapy had no reactivation after a median of 156 days (range, 92-558 days) of follow-up. The one patient who relapsed with CMV retinitis had experienced an increase in HIV RNA level and a fall in CD4+ cell count suggesting that failure to control HIV replication ultimately led to a loss of protection against CMV. Another important observation made in these patients with CMV retinitis who had responded to antiretroviral therapy was the finding of retinal inflammation with vitritis and macular edema suggesting an enhanced local immune response. This inflammatory response subsided with corticosteroid therapy. From this same group, Torriani described CMV-specific proliferative responses in vitro among 4 of the 8 patients. The patients with the most robust responses tended to be the ones in whom HIV replication was best controlled (Abstract 747). Taken together these findings suggest that pathogen-specific immunity can be restored with combination antiretroviral therapy, but that an inflammatory component may be protracted and require corticosteroid therapy.

Inflammatory manifestations of MAC were reported during early protease inhibitor therapy at last year’s conference. This year there was a report of acute worsening of symptoms of MAC with unusual manifestation (cutaneous nodules, subcutaneous granulomas) in patients with established MAC who began protease inhibitor therapy (Abstract 726). These syndromes were characterized as “reversal reactions” similar to what has been described in leprosy and were attributed to improved immunity. These complications improved with antiinflammatory therapy. Further evidence of restored immunity was demonstrated by the preliminary results of a study of discontinuation of MAC therapy conducted by Aberg and colleagues (Abstract 729). Four patients with prior disseminated MAC who completed 12 months of MAC therapy and who had a CD4+ cell count of at least 100 cells/μL and HIV RNA level less than 10,000 copies/mL after potent antiretroviral therapy discontinued MAC therapy. At an average of 6 months of follow-up after MAC treatment was discontinued, none of these patients had a recurrence of MAC disease. Further follow-up and a larger study are planned to determine the immunologic correlates of protection against relapse in patients with a history of established MAC.

**Effect of Opportunistic Infections on HIV Disease**

Reports on the effects of OIs on HIV disease extended observations presented at last year’s conference. A transient increase in plasma HIV RNA level had been previously observed in patients developing PCP or bacterial pneumonia. Morris and colleagues presented a study on the natural history of HIV RNA levels in patients undergoing treatment for pulmonary tuberculosis in Africa (Abstract 259). These patients did not receive antiretroviral therapy. Plasma HIV RNA levels were 5.6, 5.7,
5.4 and 5.4 log copies/mL at months 0, 1, 3, and 6 of tuberculosis treatment, respectively. Seventy-four percent of patients had no change in viral load, 11% experienced an increase, and 15% had a decrease in plasma viral load. Although there were data for only 19 of the 115 patients at the 6 month time point, more robust data from the earlier time points demonstrated that plasma HIV RNA levels did not uniformly decrease in patients undergoing tuberculosis treatment, despite clinical improvement. This report suggests that treatment and improvement of OIs is not invariably associated with prompt reductions in HIV RNA levels. Immune responses to infection may have variable effects on the cellular activation necessary to sustain productive HIV infection.

A similar study evaluating effects of herpes simplex virus (HSV) on HIV RNA levels was presented by Schacter (Abstract 259). The investigators instructed a cohort of HSV-infected patients in Seattle. Specimens from the mouth and genital areas were obtained daily, and were cultured for HSV. Culture results were correlated with plasma HIV RNA levels. A subset of these patients were empirically treated with acyclovir after an 8 week period of observation to determine if the prevention of HSV shedding or clinical disease influenced plasma HIV RNA levels. Although one half of the patients were reportedly on dual-nucleoside therapy, none of the study participants was receiving potent antiretroviral therapy. Nine percent of patients had clinical herpes infection and 3% had subclinical shedding. Plasma HIV RNA levels were higher during these episodes. In addition, the incidence of HSV reactivation during the observation period (15%) and plasma HIV RNA levels were significantly higher than during the acyclovir treatment period, during which no cases of clinical HSV developed. If in fact HSV symptomatic or asymptomatic infection enhances HIV replication which in turn accelerates HIV disease progression, these results offer a potential explanation to the long debated observation that acyclovir offers a survival advantage in the HIV infected population.

PREVENTION AND TREATMENT OF OIs

Much less intensive research efforts are currently being directed at treatment and prevention of OIs in part due to the declining frequency of these infections and in part due to availability of effective regimens for many common infections. Nevertheless, as illustrated by several presentations at the Conference, there is ample room to improve the effectiveness of prophylaxis with new and simplified strategies, as well as to increase the therapeutic options for serious OIs such as CMV.

Short-course prophylaxis for tuberculosis was evaluated in a randomized trial presented by Gordin and colleagues (Abstract LB5). In this 6-year trial conducted in North and South America, 1583 HIV-infected subjects with reactive tuberculin skin tests were randomized to either a one year course of daily isoniazid 300 mg or a two-month course of daily rifampin 600 mg and pyrazinamide 20 mg/kg. The median CD4+ count was 454 cells/µL and the mean follow-up time was 3 years. Rates of confirmed or probable tuberculosis were identical in the two arms. There was no difference in mortality between the arms. Completion of therapy was significantly higher in the 2-month (80%) versus the 6-month (68%) regimen. These results suggest that a 2-month, two-drug regimen is as effective as the currently recommended one-year isoniazid course. This simplified regimen may be more amenable to programmatic implementation; however, rifampin cannot be administered with HIV protease inhibitors and thus short-course prophylaxis may be limited in some situations.

A novel approach to CMV therapy using the antisense oligonucleotide fomiviren was reported by Muccioli and colleagues (Abstract LB6). In this study, AIDS patients with previously untreated zone 2 or 3 retinitis were randomized to immediate therapy or to deferred treatment. The median time to CMV retinitis progression was 71 days in the immediate therapy group versus 14 days in the deferred treatment arm. In general, fomiviren, which must be administered via intravitreal injection, was well tolerated. Transient increases in intraocular pressure and mild inflammation were noted but were not dose-limiting. The optimal role of fomiviren in new cases of CMV and disease due to relapse will need to be defined through additional clinical study.

Treatment of CMV neurologic disease was the focus of a presentation by the NEUROCMV group from Paris led by Katlama. This study represented the first prospective cohort study of patients with central nervous system (CNS) CMV infection. Patients with encephalitis or myelitis received combination induction twice-daily ganciclovir and foscarin for 3 to 6 weeks, followed by once-daily maintenance therapy. Seventy-four percent of patients had partial or complete clinical response to this regimen, and 26% had CMV disease progression that led to death. Drug toxicities were very frequent and required at least temporary discontinuation of one of the drugs in 68% of patients. Only about half of the patients were still alive after 3 months of therapy, and the outcome was improved with longer duration of combination therapy. Despite the grim survival data, dual-therapy still appeared more favorable than historical monotherapy data. Potent antiretroviral therapy was not available during the course of this
study and one might expect this intervention to have a potentially favorable outcome on the natural history of this CMV disease.

Kaposi's Sarcoma

Recent advances in our understanding of the epidemiology of Kaposi's sarcoma (KS) were summarized by Ganem in a plenary session. First-generation serologic assays measuring antibody to antigen expressed on KS-associated herpesvirus (KSHV) latently-infected cells suggested that the seroprevalence is 1% to 2% in HIV-uninfected blood donors. Second-generation assays measuring an antigen expressed during lytic infection estimate slightly higher (i.e., 6%) seroprevalence in this population. With this later assay, seroprevalence for KSHV was found to be 60% in a male gay population and 97% in a Baltimore cohort of patients with KS (Abstract 439).

In retrospective studies evaluating KSHV antibody in longitudinal cohorts, it appears that infection with KSHV precedes clinical disease and that the presence of antibody is associated with an increased risk of disease. In a San Francisco cohort of 185 HIV-infected men with evidence of KSHV infection, the probability of developing KS was 50 percent at 10 years (Abstract 430). Studies demonstrating that the risk of acquisition of KSHV infection is associated with the development of other sexually transmitted diseases argues that KSHV infection is acquired via sexual exposure. Pediatric KSHV was evaluated in a Zambian study. A seroprevalence of 39% was reported among Zambian women and the seroprevalence of KSHV was 29% in offspring of those women with KS. All three children with KS had mothers with KSHV antibody (Abstract 526).

KSHV infection targets spindle cells and the infection remains latent in most cases. It is estimated that only 5% of infected cells are in a lytic state. The preponderance of data would suggest that infection with KSHV is a necessary but not sufficient event in the pathogenesis of KS. Bais reported that a KSHV G protein coupled receptor is a viral oncogene that can induce cell signaling pathways to enable angiogenesis and cell transformation (Abstract 527).

There was sparse new information on therapeutic approaches for KSHV. Carr described a local inflammatory reaction at the site of cutaneous KS lesions after the initiation of ritonavir therapy. He speculated this reaction was due to improved immunity to KSHV (Abstract 528). Others reported improved long-term outcomes of KS associated with reductions of plasma HIV RNA levels and immune improvement produced by potent antiretroviral therapy (Abstracts 431, 434). Looney used polymerase chain reaction (PCR) assays to quantitate KSHV in peripheral blood mononuclear cells and found that higher KSHV burden in patients with visceral versus cutaneous-only disease, as well as a decline in KSHV levels after administration of chemotherapy (Abstract 525).

HIV in Women

This year's conference featured several poster sessions that focused on issues related to HIV-infected women. A number of groups reported on efforts to isolate and identify HIV from genital secretions (Abstracts 709-714). While there is no consensus on the optimal method for collecting or analyzing genital tract specimens, it appears that virus can be readily detected using a variety of methods. Comparisons of HIV genotypes isolated from genital tract and blood revealed conflicting results. Data from Shaheen et al (Abstract 710) identified a similar genotype among isolates from the blood and genital tract while Subbarao (Abstract 708) found differences in the major species of HIV in vaginal secretions compared to blood in 2 of 4 women studied suggesting local HIV expression in the genital tract. Further work including larger numbers of subjects will be needed to resolve this issue. Other important observations included the finding of a direct correlation between plasma and genital tract viral load (Abstract 712), a reduction in genital tract viral load during antiretroviral therapy (Abstract 713) and the suggestion of a correlation between plasma viral load and rates of cervical dysplasia (Abstracts 716, 258).

Neurologic Complications

Despite advances in HIV therapy, peripheral neuropathy remains a common problem that can be difficult to treat. One approach to treatment has included acupuncture, which was evaluated in a randomized trial reported by the CPCRA. In a four-year study, 250 patients were randomized to receive acupuncture or control points, amitriptyline versus placebo, or both in a factorial design. After 16 weeks of treatment no differences were seen in relief of pain with either acupuncture or amitriptyline compared with the placebo groups. The results of this study add acupuncture and amitriptyline to the long list of ineffective therapies for peripheral neuropathy.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the brain caused by the JC polyomavirus. In a comprehensive review, Major discussed the pathogenesis of PML and reviewed data suggesting that PCR for JC DNA from cerebrospinal fluid (CSF) correlates with a tissue diagnosis of PML in the brain in 75% of cases. Rates of PML appear to be declining along with other OIs. However, in the French series of OIs, the rate of decline for PML was the lowest over-
all (Abstract 182). Again at this year's conference, reports indicated that potent combination antiretroviral therapy including a protease inhibitor could improve the outcome of PML in some patients (Abstracts 463, 464, 465). The need for better specific therapy for PML was highlighted by a report from Pillero et al, who described two patients who developed PML while receiving protease inhibitor therapy and did not respond to changes in their antiretroviral therapy (Abstract 466). One agent that has been considered for PML therapy is cidofovir and a report of PML treated with cidofovir was presented by Matheson et al (Abstract 457). In this series of seven cases of PML diagnosed by CSF PCR or brain biopsy (all patients were on protease inhibitor-containing therapy) the response was variable. Three patients improved, two stabilized, and two worsened. These initial results suggest that further evaluation of cidofovir for PML may be warranted.

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**Update on Developments in Antiretroviral Therapy**

Roger T. Inouye, MD  
Scott M. Hammer, MD

Studies detailing the recent advances in antiretroviral chemotherapy comprised a major component of the 5th Conference on Retroviruses and Opportunistic Infections. Among the most important positive themes were the durability of potent regimens that can be achieved with currently available combination regimens, their immunologic and clinical benefits, the marker comparability of more simplified dosing schedules compared with standard dosing regimens, the increasing permutations of effective combinations, and the promise of new agents. Amidst the generally positive and optimistic messages, cautious notes were also sounded. These included the incomplete response rate to current combination regimens, the threat of cross-resistance within existing drug classes, the urgent need for effective salvage regimens, the negative results of the initial trials of induction-maintenance strategies, and the emergence of longer-term toxic effects in individuals exposed to protease inhibitors. The balance reflected at the meeting cast an appropriate perspective on the rapidly changing field of HIV care and clinical research.

**Initial Therapeutic Options**

**Protease Inhibitor-Based Options**

**Protease inhibitor/nRTI therapy.**—While several studies elucidated the pharmacokinetic, efficacy, tolerability, and resistance patterns of investigational protease inhibitors, numerous studies of the use of approved protease inhibitors (ie, saquinavir, ritonavir, indinavir, nelfinavir) were also presented. These data sets include (1) extended follow-up of previously reported clinical trials; (2) clinical efficacy comparisons of regimens based on protease inhibitors combined with nucleoside analogue reverse transcriptase inhibitors (nRTIs) in less frequent dosing schedules; (3) efficacy of a new formulation of saquinavir (soft gelatin capsule, SGC); and (4) unique protease inhibitor-specific adverse effects and drug interactions.

**Extended Clinical Trial Follow-Up**

The 84-week follow-up of the Merck 039 study was presented by Hirsch et al (Abstract 383). This was a randomized double-blind trial that enrolled zidovudine-experienced patients with CD4+ cell counts <500/μL (median, 150/μL) and a median plasma HIV-1 RNA level of 89,510 copies/mL and compared indinavir/zidovudine/lamivudine with indinavir or zidovudine/lamivudine for 24 weeks after which time all patients received open-label indinavir/zidovudine/lamivudine. At week 84, patients who were originally randomized to the 3-drug combination had a median plasma HIV-1 RNA reduction of 1.98 log, versus 1.35 log and 1.32 log reductions for those who had received initial indinavir monotherapy or dual nRTI therapy, respectively.

Clewenin et al presented an analysis of the extended follow-up of the Agouron 511 protocol (Abstract 372). This study enrolled antiretroviral-naive patients with a mean baseline plasma HIV-1 RNA level of 4.9 loge and a CD4+ cell count of 283 cell/μL. After 12 months, nelfinavir, administered at the standard 750 mg po tid dose combined with zidovudine and lamivudine resulted in a mean 2.9 log reduction in plasma viral level. Of these subjects, 62% had decreases in plasma HIV-1 RNA levels to below 50 copies/mL.

In the AVANTI 3 clinical trial, nelfinavir/zidovudine/lamivudine was compared with zidovudine/lamivudine in antiretroviral-naive patients with baseline CD4+ counts between 150 and 500 cells/μL (Abstract 8). After 28 weeks of therapy, the median log area-under-the-curve-minus baseline (AUCMB) value for the triple-drug arm was statistically greater than for the dual nRTI arm (1.85 log reduction versus 0.98 log reduction). Approximately 50% of the former group had reductions in plasma levels to below 40 copies/mL versus about 10% of the latter group. Markowitz et al also presented data on the efficacy of nelfinavir/zidovudine/lamivudine (Abstract 371) in a group of antiretroviral-naive subjects with mean baseline CD4+ cell count and plasma HIV-1 RNA level of 258/μL and 5.32 log respectively. This regimen resulted in a mean increase in total CD4+ cell counts of 160/μL. At 24 months, 11 of 12 evaluable subjects had a plasma HIV-1 RNA level below 500 copies/mL. Nelfinavir trough levels measured in the first year of therapy were not found to be predictive of the duration of response.

Katlama et al presented data from the ALTIS-PLUS study, an extension of the ALTIS 1 and 2 clinical trials that evaluated the 24-week efficacy of stavudine/lamivudine in antiretroviral naive and experienced subjects, respectively (Abstract 376). After the initial ALTIS 1 and 2 study period, ritonavir was added to patients' regimens if their plasma HIV-1 RNA level was greater than 200 copies/mL. At week 34, 75% and 50% of subjects who added ritonavir to their stavudine/lamivudine regimen had decreases in plasma HIV-1 RNA levels to
below 3000 and below 200 copies/mL, respectively. However, by week 50, these percentages diminished to 48% and 35%, respectively, suggesting that the simple addition of ritonavir to a prior regimen failed to confer a durable virologic response in most subjects.

Comparisons of Protease Inhibitor/ Dual nRTI Regimens

Comparisons of different protease inhibitors combined with the same dual nRTI regimen included an open-label randomized trial presented by Martinez et al. The study compared the efficacy of indinavir, ritonavir, or hard-gelatin capsule saquinavir, each in combination with stavudine/lamivudine in patients in whom nRTI therapy had failed (Abstract 370). After 6 months, the mean log reductions in plasma HIV-1 RNA levels were 1.7, 2.2, and 1.3, respectively. In these three groups, 50%, 60%, and 30% had decreases in plasma HIV-1 RNA levels to below 200 copies/mL, respectively. While the saquinavir-based regimen was statistically less effective, it was better tolerated than the regimens containing indinavir or ritonavir. In a related study by Clumeck et al, there was no statistically significant difference between protease inhibitor-naive subjects who received indinavir or who received ritonavir in virologic, immunologic, or the endpoints of survival and AIDS-defining illness (Abstract 386). Similarly, in the CHEESE study, a multicenter open-label randomized trial among patients with a mean baseline CD4+ cell count of 300/L and a baseline plasma HIV-1 RNA level of 4.95 log, there was no significant difference in virologic response between the group taking zidovudine/lamivudine/indinavir and the group taking zidovudine/lamivudine/saquinavir soft gelatin capsule (Abstract 387b).

Various studies also compared the relative efficacies of specific dual- nRTI regimens paired with the same protease inhibitor (Abstracts 378, 379, 380, 381). These trials reported similar virologic responses using stavudine/lamivudine, stavudine/didanosine, or zidovudine/lamivudine combined with indinavir.

Efficacy of Newer Formulations and Agents

In an attempt to create dosing schedules that might enhance adherence, studies were conducted of protease inhibitor-based combinations comparing bid with tid schedules of administration. Nelfinavir, administered at 1250 mg bid or 750 mg tid combined with stavudine/lamivudine or zidovudine/lamivudine was assessed in two studies (Abstracts 373, 387a). Virologic and immunologic responses up to 32 weeks of therapy were comparable among the dosing groups, as was tolerability. Similarly, indinavir dosed at either 1000 mg or 1200 mg bid yielded at least comparable virologic responses and adverse event rates, compared with 800 mg tid, combined with zidovudine/lamivudine at week 32 (Abstract 374).

Eron et al compared the clinical efficacy of the recently FDA approved fixed-dose formulation of zidovudine/lamivudine with conventionally formulated, separate zidovudine and lamivudine (the regimens included a protease inhibitor). Virologic responses were similar between the study groups (Abstract 387c).

Data were presented using the recently approved soft gelatin capsule (SGC) formulation of saquinavir, which possesses a 10-fold increased oral bioavailability over the original formulation. The virologic and immunologic effects of the initial hard gelatin capsule formulation and the soft gelatin version were compared, with each group also taking two nRTIs (Abstract 368). After 16 weeks of therapy, 47% of the saquinavir SGC-assigned group versus 28% of the hard gel capsule group had reductions in plasma HIV-1 RNA levels to below 50 copies/mL from the baseline mean of 4.8 log. In another study, saquinavir SGC combined with zidovudine/lamivudine resulted in a median reduction in plasma HIV-1 RNA levels of 3.31 log; 70% had <20 copies/mL at week 32 (Abstract 369).

Dual Protease Inhibitor Therapy

The rationale for antiretroviral therapy with two protease inhibitors includes additive or synergistic antiretroviral effects; favorable pharmacokinetic interactions resulting in less intensive dosing schedules; and where possible, non- or partially overlapping resistance patterns. Pharmacokinetic, safety, and efficacy data related to the use of a number of dual protease inhibitor regimens were presented at the Conference.

Ritonavir/saquinavir.—Studies that examined the safety, efficacy, and durability of this, the most studied of dual protease inhibitor combinations, included a presentation by Cameron et al of a dose-ranging open label study of 141 antiretroviral naive individuals with CD4+ cell counts between 100 and 500 cells/μL who received ritonavir/saquinavir with or without 2 nRTIs (19% added 2 nRTIs) (Abstract 388). After 60 weeks of therapy, 89% of patients remaining on study decreased their plasma HIV-1 RNA levels to < 200 copies/mL from a mean pretreatment of approximately 4.5 log copies/mL. The 400-mg bid dosing for both the ritonavir and the saquinavir was the best tolerated of the regimens tested. The most common adverse events were liver enzyme and triglyceride elevations. In a second study by Gisolf et al, ritonavir/saquinavir was compared with ritonavir/saquinavir/stavudine in protease inhibitor- and lamivudine-naïve
subjects with a mean pretreatment plasma HIV-1 RNA level of 4.3 log and CD4+ cell count of 260 cells/μL (Abstract 389). At week 24, a trend favoring the 3-drug regimen was seen with 87% in the 3-drug study group having plasma HIV-1 RNA reductions to <400 copies/mL compared with 64% of those in the dual- protease inhibitors alone group. At week 12, a subanalysis of cerebrospinal fluid (CSF) viral load responses showed that 1 of 3 patients who received ritonavir/saquinavir had viral RNA levels in the CSF reduced to below the level of detection, compared with 4 of 5 of the patients who received ritonavir/saquinavir/stavudine. A notable pharmacokinetic finding was that both ritonavir and saquinavir CSF levels were unmeasurable.

**Indinavir/nelfinavir**— Results from a clinical trial employing a twice-a-day dosed indinavir/nelfinavir regimen (1000 mg and 750 mg, respectively) were reported by Kerr et al (Abstract 393). In this study, protease inhibitor-naive subjects with pretreatment plasma HIV-1 RNA levels above 30,000 copies/mL and CD4+ counts above 100 cells/μL were enrolled. In a pharmacokinetic analysis of this combination compared with historical indinavir and nelfinavir monotherapy data, the indinavir/nelfinavir combination resulted in similar indinavir systemic exposure, but lower nelfinavir trough levels. Increasing the nelfinavir dose to 1000 mg bid improved this deficiency. At week 32 there was a median CD4+ cell increase of 133 cells/μL; in 10 of 21 patients the plasma HIV-1 RNA level was <400 copies/mL and in 6 of 10 it was <50 copies/mL. The most common adverse effect was diarrhea, which occurred in 6 patients.

**Nelfinavir/ritonavir**— Gallant et al presented preliminary data on the safety and efficacy of nelfinavir/ritonavir in protease inhibitor-naive patients. The median baseline plasma HIV-1 RNA level was 32,459 copies/mL and the median CD4+ cell count was 325 cells/μL (Abstract 394a). Ritonavir was dosed at 400 mg bid and nelfinavir at either 500 mg or 750 mg bid. Diarrhea was the most common adverse effect, occurring in 9 of 20 patients. At week 16, reductions in plasma viral levels of greater than 2 log were seen.

**Nelfinavir/Saquinariv SGC.—** Two studies reported on the use of nelfinavir/saquinavir SGC in protease inhibitor-naive individuals. Opravil, on behalf of the SPICE Study Team, presented the 32-week results of a clinical trial that examined the efficacy of nelfinavir 800 mg tid/saquinavir SGC 750 mg tid, with or without 2 nRTIs relative to either of these two protease inhibitors combined with nRTIs in subjects with a mean pretreatment plasma HIV-1 level of 4.7 log (Abstract 394b). After 32 weeks of therapy, 36% of patients randomized to receive the 4-drug regimen had plasma HIV-1 RNA levels <50 copies/mL, compared with 40% in the nelfinavir/saquinavir SGC alone group, and 20% of those who received either nelfinavir or saquinavir SGC combined with 2 nRTIs. A separate study evaluated nelfinavir/saquinavir SGC at the same dosing schedule with up to two nRTIs. The group of 14 subjects had a median pretreatment plasma HIV-1 RNA level of 39,917 copies/mL and a median CD4+ cell count of 327/μL; there was a median log decrease in HIV-1 viremia of 2.4 at week 52 (Abstract 394c).

**Protease Inhibitor Drug Interactions and Adverse Effects**

Notable protease inhibitor pharmacokinetic interactions described at the Conference are summarized in the table.

### Protease Inhibitor-Related Adverse Effects

Reported adverse effects associated with protease inhibitors included several descriptions of altered lipid and carbohydrate metabolism (Abstracts 407–416). This syndrome is characterized by focal fat redistribution, hyperlipidemia, and insulin resistance. It may occur earlier and be more severely in patients who are taking dual protease inhibitor (ie, ritonavir/saquinavir) regimes (Abstracts 407–414). The frequency of this lipodystrophy is not yet clear. Protease inhibitor-related hepatitis and renal interstitial fibrosis were also reported (Abstracts 417, 418).

### NNRTI-containing Regimens

Numerous studies provided pharmacokinetic, resistance, and clinical efficacy data related to the use of nonnucleoside reverse transcriptase inhibitors (NNRTIs) in combination with dual nRTIs or with protease inhibitor/nRTI regimens.

**Delavirdine**— In a mostly antiretroviral naive study group with a mean pretreatment plasma HIV-1 RNA level of 4.5 log and CD4+ cell count of 354 cells/μL, Sargent et al reported that a regimen consisting of delavirdine/zidovudine/lamivudine resulted in a mean plasma viral RNA reduction of >2 log through week 32, with 60% of recipients having their HIV-1 RNA levels below 400 copies/mL; 50% of these subjects had levels below 40 copies/mL. Achieving a level below the 40 copies/mL limit of detection correlated better with long-term viral suppression than did reaching below
<table>
<thead>
<tr>
<th>Protease inhibitor</th>
<th>Second antiretroviral drug</th>
<th>Interaction</th>
<th>Reciprocal interaction</th>
<th>Abstract number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>Delavirdine</td>
<td>No significant delavirdine AUC change</td>
<td>Ritonavir AUC increased by 70%</td>
<td>340</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Delavirdine</td>
<td>Delavirdine AUC reduced by 40%</td>
<td>Nelfinavir AUC increased by 100%, but hydroxy-nelfinavir (active metabolite) AUC decreased by 50%</td>
<td>345</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Nevirapine</td>
<td>No significant nevirapine AUC change</td>
<td>Differing results of nevirapine effects on nelfinavir AUC in two studies: either unchanged (Abstract 351) or decreased by 46% (Abstract 350)</td>
<td>360, 351</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Saquinavir hard gelatin capsule</td>
<td>Increased saquinavir AUC by 13-fold</td>
<td>Not reported</td>
<td>352, 353</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Saquinavir soft gelatin capsule</td>
<td>Saquinavir AUC increased by 392%</td>
<td>No significant changes to nelfinavir AUC noted</td>
<td>354</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Saquinavir soft gelatin capsule</td>
<td>Saquinavir AUC increased by 620%</td>
<td>No significant changes to indinavir AUC noted</td>
<td>354</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Nelfinavir</td>
<td>Nelfinavir AUC increased by 150%</td>
<td>No significant changes to ritonavir AUC</td>
<td>394a</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Saquinavir soft gelatin capsule</td>
<td>Saquinavir AUC increased by 20-fold</td>
<td>No significant changes to ritonavir AUC note</td>
<td>354</td>
</tr>
</tbody>
</table>

AUC indicates area-under-the-curve.

the 400 copies/mL threshold (Abstracts 694, 699).

Delavirdine susceptibilities were determined from ACTG 261, a randomized, double-blind clinical trial that compared delavirdine/zidovudine/didanosine; delavirdine/zidovudine; and delavirdine/didanosine (Abstract 706). Resistance to delavirdine was delayed in the triple-drug arm, relative to the dual-drug arms. Moreover, genotypic resistance patterns varied with the addition of the nRTIs. For example, the Y181C mutation developed only in the isolates from subjects in the delavirdine/didanosine arm; the P236L mutation was seen occasionally and transiently in patients in the delavirdine/zidovudine group; the K103N mutation occurred with even distribution among the three study arms.

Nevirapine.— Initial therapy with nevirapine-containing regimens was evaluated in a number of studies. The long-term follow-up of subjects from the INCAS trial demonstrated continued marker responses (median plasma HIV-1 RNA decrease of 2.55 log and CD4+ cell increase of 151/μL) for more than 130 weeks (Abstract 695). In a separate study, nevirapine/stavudine/lamivudine treatment was evaluated in a group of 25 antiretroviral-naïve patients with a mean pretreatment plasma HIV-1 RNA level of 160,000 copies/mL and CD4+ cell count of 259 cells/μL. Through week
44, 88% of subjects remaining in the study had plasma HIV-1 RNA levels <400 copies/mL (Abstract 690). A study of nevirapine/indinavir in antiretroviral-naive patients with a mean pretreatment CD4+ cell count of 342 cells/μL and plasma HIV-1 RNA level of 4.8 log was presented by Beach et al.Investigators noted >2 log decrease in plasma viral load at week 24 (Abstract 428).

The marker and histologic responses resulting from the use of nevirapine in combination with indinavir/zidovudine/lamivudine in antiretroviral-naive subjects were evaluated by Polis et al (Abstract 394). In a small study group of 7 patients, plasma HIV-1 RNA level reductions between 1.5 and 3.5 log were documented within 15 days after treatment initiation. Abnormal lymph node architecture also was noted to improve with treatment as evidenced by re-established germinal centers.

nRTI-Based Therapy

Although alone they are no longer considered standard therapies, dual nRTI combinations are pivotal components of three- and four-drug regimens. As such, several studies demonstrated characteristics of specific dual nucleoside combinations that have relevance to current combination therapy. Kuritzkes, on behalf of the ACTG 306 Study Team, reported 48-week data showing that there was no statistical difference between the virologic effects of zidovudine or stavudine combined with lamivudine (1.01 versus 1.08 log reduction in plasma HIV-1 RNA, with 12% versus 4% of subjects achieving plasma viral loads <50 viral copies/mL, respectively) in antiretroviral-naive subjects. The mean pretreatment viral load of the group was 4.01 log copies/mL (Abstract 1). Moreover, the addition of lamivudine did not increase antiretroviral effects of didanosine monotherapy.

In agreement with previously reported in vitro antagonism between zidovudine and stavudine, Havlir and her colleagues of the ACTG 290 and 298 Study Teams concluded that zidovudine/stavudine resulted in comparable or inferior responses compared with stavudine monotherapy; the combination therefore, should be avoided (Abstract 2). Of note, it was also observed that prior zidovudine use diminished the efficacy of subsequent stavudine use and that didanosine resulted in a greater plasma HIV-1 RNA decrease than stavudine over a 48-week period (a 0.44 log reduction versus a 0.13 log increase, respectively).

Cellular Inhibitor Combinations: Hydroxyurea Combinations

Further encouraging data regarding the use of hydroxyurea, a cellular ribonucleotide reductase inhibitor, in combination with nRTIs and/or protease inhibitors were presented. In a late-breaker session, Lori et al reported the results of a study using a combination of hydroxyurea/indinavir/didanosine in primary HIV infection. A potentially important mechanism of action of hydroxyurea in this clinical setting may be to block cell activation and thus limit viral targets and viral production. After a mean follow-up time of 11.3 months, all 24 patients in the trial had plasma HIV-1 RNA levels below 500 copies/mL, from a mean pretreatment level of 455,700 copies/mL for the group (Abstracts LB11, 655). On this regimen, total CD4+ cell counts increased by a mean of 168/μL; naive CD4+ cell counts increased significantly as well. Intriguingly, after withdrawal of the drug, plasma HIV-1 RNA rebound was not seen in one of these patients for more than 12 months, although infectious virus was recoverable from this individual.

Several groups presented the virologic and immunologic effects of hydroxyurea combined with stavudine and didanosine (Abstracts 653, 654,656,657). Rutschmann et al employed this regimen in 144 subjects (75% were antiretroviral naive; the mean pretreatment plasma HIV-1 RNA level was 4.5 log and CD4+ cell count was 370/μL). Subjects were randomized to receive stavudine/didanosine plus hydroxyurea or placebo (Abstract 656). After 12 weeks, significantly more subjects who received hydroxyurea had less than 200 and less than 20 copies of HIV RNA/mL of plasma. In terms of adverse effects, in a separate study, reversible neutropenia developed in patients who had pretreatment absolute neutrophil counts below 1700/μL (Abstract 653).

INVESTIGATIONAL DRUGS

Investigational nRTIs

Abacavir (1592U89).—A number of studies were presented that further characterized the pharmacokinetics, safety, resistance profile, and efficacy of abacavir, a highly active carbocyclic guanosine analogue.

Pharmacokinetic studies revealed that abacavir is primarily metabolized through nonmicrosomal pathways to glucuronide and carboxylic acid metabolites and, therefore, should not interact with the cytochrome P450-mediated metabolism of protease or non-nucleoside reverse transcriptase inhibitors (Abstract 634). Adequate abacavir CNS penetration was suggested by Ravitch et al who demonstrated mean cerebrospinal fluid (CSF) levels that were twice the 50% inhibitory concentration (IC50) of the drug (Abstract 636). Among adverse effects associated with abacavir, the most significant is a hypersensitivity reaction, noted in approximately 3% of cases. It has a median onset of 9 days (range, 3-42 days) after initiation.
of the drug (Abstract 4). This reaction is characterized by fever, malaise, nausea and vomiting, myalgias, arthralgias, and occasionally, diarrhea. Rash is common but is not always seen. Liver enzyme and creatine kinase elevations have also been noted. These symptoms typically resolve within 1 to 2 days after the drug is discontinued. If this syndrome is suspected, abacavir should be discontinued, and rechallenge with the drug is contraindicated because of the risk of a life-threatening reaction.

In work presented by Tremblay et al, this compound maintained activity in vitro against zidovudine-resistant HIV-1 isolates (albeit, 2- to 5-fold higher IC₅₀ than in zidovudine-susceptible isolates) synergistically with zidovudine, nevirapine, and amnepnavir; and additive or synergistic effects with didanosine, stavudine, zalcitabine, and lamivudine (Abstract 632). The authors further noted that abacavir synergized with zidovudine-lamivudine against zidovudine-susceptible and -resistant strains.

The resistance mutations in the RT gene selected in vitro by abacavir at residues 65, 74, 115, and 184 were noted in an isolate selected in vivo, as reported by Larnier and the Abacavir Investigative Team (Abstract 686). This genotype was associated with a threefold increase in the viral IC₅₀. Other substitutions were noted with greater losses of susceptibility to the drug. In a separate study by Mellors et al, more than 90% of HIV-1 isolates that were resistant to zidovudine, lamivudine, or zidovudine/lamivudine remained susceptible to abacavir in vitro (Abstract 687); however, the virologic responses in patients with these isolates were less encouraging. Resistant isolates with loss of susceptibility to additional nRTIs, however, were less likely to retain susceptibility to abacavir. In this and the prior study, baseline phenotypic resistance more than eightfold above the wild-type IC₅₀ was predictive of a poor virologic response at 4 weeks of therapy.

Data for the triple-nRTI regimen abacavir/zidovudine/lamivudine were presented by Staszewski et al. Among antiretroviral-naïve subjects who received this open-label combination, 60% had plasma HIV-1 RNA levels below 400 copies/mL and 48% had fewer than 50 copies/mL at 48 weeks, (the median baseline level was approximately 5 log) (Abstract 658). In a separate study also reporting antiretroviral effects of abacavir in combination with other antiretrovirals including nRTIs, 8 of 15 patients had plasma HIV-1 RNA levels <400 copies/mL at 48 weeks (Abstract 659).

Results from trials using abacavir in combination with protease inhibitors were also presented. Mellors et al reported data collected from the CNA2004 Trial, which enrolled 80 antiretroviral-naïve subjects (median plasma HIV-1 RNA levels and CD4+ cell counts of 4.74 log and 349/µL, respectively), who were randomized to receive abacavir combined with amnepnavir, indinavir, ritonavir, saquinavir SGC, or nelfinavir (Abstract 4). After 16 weeks on therapy, between 50% and 85% of subjects had plasma HIV-1 RNA levels <400 copies/mL, and 40% to 70% had <50 copies/mL. Immunologic changes included approximate median absolute increases of 160 total CD4+ cells/µL, 20 naive CD4+ cells/µL, and 100 memory CD4+ cells/µL from baseline at week 16 (Abstract 364).

FTC.—Pottage et al presented data on the efficacy of the cytidine analogue, FTC (LB9). In vitro studies have shown that FTC is synergistic with zidovudine, stavudine, efavirenz, MKC-442, an NNRTI, indinavir, and nelfinavir. In this phase I/II clinical trial, patients with mean baseline HIV-1 RNA levels between 4.2 and 4.7 log received FTC at oral doses of either 25 mg or 200 mg bid. At the higher dose, plasma viremia was reduced by an average of 2.1 log after 14 days without significant adverse effects.

Nucleotide Analogue Reverse Transcriptase Inhibitors

Adefovir.—A study of adefovir-resistant (bis-pom-PMEA) isolates selected in vivo presented by Miller et al demonstrated K70E and T69D mutations in the RT gene (Abstract 677). The K70E genotype was associated with a 2- to 3-fold decrease in virus susceptibility to adefovir. This genotype showed 4.9-fold and a 2.7-fold decreases in PMEA and lamivudine susceptibility, respectively. The presence of the M184V mutation in high-level zidovudine/lamivudine-resistant isolates reversed PMEA resistance by 2.6 to 4.4-fold. The significance of this resistance mutational interaction is unclear.

PMPA.—Wainberg et al demonstrated that in vitro selection of PMPA resistance resulted in K65R mutation with a 3-fold increase in IC₅₀ and moderate cross-resistance to zalcitabine, didanosine, lamivudine, and adefovir (Abstracts 630,680). HIV-1 strains resistant to zidovudine, didanosine, or multiple nRTIs (containing the Q151M gene complex) remained susceptible to PMPA. Similar to PMEA, isolates containing the lamivudine-associated M184V substitution had increased susceptibility to PMPA (Abstracts 677,680).
Deeks et al presented phase I/II bis-poc-PMPA dose-escalation data (LB8). The oral bioavailability of this drug is 41% when taken without food (reduced to 27% when taken with food) and it has a half-life of more than 17 hours. In initial clinical efficacy studies, plasma HIV-1 RNA levels returned to pretreatment values in all doses studied by day 60 of treatment in patients with a baseline CD4 cell count of 375 cells/μL and plasma HIV-1 RNA level of 4.5 log Significant adverse effects included elevations in transaminases and creatine kinase.

NNRTIs

Efavirenz (DMP 266)—. From two studies, DMP 266-005 and DMP 266-003, data were presented on efavirenz combined with two nRTIs or a protease inhibitor (Abstracts 692,698). When efavirenz at 600 mg/d, was taken with zidovudine and lamivudine by antiretroviral-naive individuals for 24 weeks, the mean plasma HIV-1 RNA level was diminished from a pretreatment level of 4.7 log by approximately 2 log. Ninety-percent of these patients had plasma viremia reduced to less than 400 copies/mL, and 67% to below 40 copies/mL (Abstract 698). In the DMP 266-003 study, Kahn, on behalf of DMP 266 Clinical Development Team, reported that efavirenz combined with indinavir in patients, the majority of whom (71%) had prior nRTI experience, resulted in a mean reduction in plasma HIV-1 RNA levels of 2.5 log (91% to below 400 copies/mL) and a mean increase in CD4+ cell count of 267/μL after 60 weeks of therapy (Abstract 692). Nausea, headache, and fatigue were the most commonly encountered adverse effects.

Efavirenz resistance was most commonly associated with a K103N substitution (19-fold decreased susceptibility to the drug) in both in vivo and in vitro studies (Abstracts 702,703). This mutation mediates cross-resistance to nevirapine (40-fold decrease); delavirdine (28-fold decrease); and loviride (7-fold decrease). In drug susceptibility testing, viral isolates with the NNRTI-associated resistance mutation, Y181C, and the delavirdine-associated resistance mutation P236L retained susceptibility to efavirenz (Abstract 702).

Protease Inhibitors

Amprenavir(141W94; VX-478).— Studies were presented that employed amprenavir in monotherapy or in combination with nRTIs. Murphy et al reported the results of ACTG 347, which analyzed amprenavir alone or combined with zidovudine/lamivudine in protease inhibitor- and lamivudine-inexperienced patients. The median CD4+ cell count and plasma HIV-1 RNA level was of 305/μL and 37,889 copies/mL, respectively (Abstract 512). The amprenavir monotherapy arm was discontinued after a median of 88 days due to 9 cases of early virologic failure. At 24 weeks, 63% of patients in the 3-drug arm had plasma HIV-1 RNA levels <400 copies/mL.

The efficacy of combination amprenavir/abacavir in antiretroviral-naive patients (median baseline plasma HIV-1 RNA of 4.38 log copies/mL and CD4+ cell count of 619/μL) was reported by Bart et al (Abstract 365). After 24 weeks of therapy, 9 of 11 patients had plasma HIV-1 RNA values below 50 copies/mL

A four-drug combination of abacavir/zidovudine/lamivudine/amprenavir was assessed by Kost et al in acutely (<90 days since exposure) and chronically HIV-1-infected, protease inhibitor- and lamivudine-naive subjects (Abstract 363). With mean baseline plasma HIV-1 RNA levels of 192,641 and 57,174 copies/mL, at week 20, 4 of 7 and 8 of 9 subjects lowered these levels to below 100 copies/mL, respectively. In an analysis of non-plasma viral load effects in a compartment other than plasma, CSF HIV-1 RNA levels were reduced from a mean baseline of 1,644 copies/mL and 8,093 copies/mL by 1.22 log by week 8 in the acutely-infected and chronically-infected individuals, respectively. Immunologic effects at week 12 were notable for increases in CD4+CD62L+RA+ naive cells of 106 and 29/μL, respectively.

The preliminary efficacy of amprenavir-containing dual protease inhibitor therapy was illustrated by the PROA2001 study that enrolled protease inhibitor-naive patients treated with amprenavir combined with a second protease inhibitor including indinavir, nelfinavir, and saquinavir SGC (Abstract 6). Baseline median logplasma HIV-1 RNA levels ranging from 4.45 to 5.14 were reduced by 2.53 and 3.18 log copies/mL.

The genotypic characterization of HIV-1 isolates from patients in whom amprenavir therapy was failing in the ACTG 347 study was presented by DePasquale et al (Abstract 406A). In this analysis, two classes of amprenavir monotherapy mutations were described: (1) I50V-containing isolates with associated companion mutations within the protease coding region or an associated gag cleavage site mutation (I to F substitution at the P1/P6 gag cleavage site); and (2) or alternatively, isolates with protease coding region mutations other than I50V also accompanied by gag cleavage site changes. Failure of amprenavir/zidovudine/ lamivudine combination therapy was related to the presence of the M184V lamivudine resistance associated mutation in the RT gene; substitutions in the protease coding region residues 10, 20, 46, 50, 54, and 82; or gag cleavage site changes.
PNU-140690.—Initial safety and pharmacokinetic data of PNU-140690, a potent, non-peptidic protease inhibitor of the dihydropyrimidine class with activity versus ritonavir resistant isolates were presented in two posters. In healthy volunteers, PNU-140690 systemic exposure was increased by two-fold with high-fat food and reduced by co-administration with antacids by 33% (Abstract 649). The major adverse effects were nausea, diarrhea, and abdominal cramps (Abstract 648).

Other Agents

Pre-clinical data were presented on a number of antiretroviral compounds including the reverse transcriptase inhibitors dd4FC, which lacks cross-resistance to the approved nRTIs (Abstract 629); the cyclopropane, QYL-685, which selects for a M184I mutation in vitro; BCH-10652, a 4'-thio heterosubstituted nRTI with low plasma protein binding and activity against viral strains resistant to lamivudine, zalcitabine, zidovudine, and PMEA (Abstract 628); +/-calanolide A, an NNRTI; and PD178390, a non-peptidic dihydropyrimidine protease inhibitor, which retains activity against protease inhibitor resistant HIV-1 strains with substitutions at residues G48, M46, V82, V84, and D30 (Abstracts 637,638).

TREATMENT FAILURE AND SALVAGE THERAPIES

Predictors of Response to Initial Protease Inhibitor Therapy

Demeter, on behalf of the ACTG 320 Study Team, presented an examination of predictors of virologic response (Abstract 509). The subjects were zidovudine-experienced with CD4+ cell counts 200/μL or below and were randomized to indinavir/zidovudine/lamivudine or zidovudine/lamivudine. The strongest independent predictor of week 24 and 40 viral suppression was the absolute week 4 to 8 plasma HIV-1 RNA concentration. In an analysis of predictors of immunologic response to the three-drug, protease inhibitor regimen used in ACTG 315 (ie, ritonavir/zidovudine/lamivudine), the return of a delayed type hypersensitivity reaction did not correlate with the amplitude of plasma HIV-1 RNA suppression and only weakly correlated with the degree of CD4+ cell count increase (LB14).

Antiretroviral Resistance Interactions

In part, a rational formulation of a potential salvage regimen is dependent upon a consideration of resistance and cross-resistance patterns of the antiretrovirals which comprise the failed regimen. Accordingly, there were several reports of genotypic and phenotypic resistance patterns to these agents alone and in combination with other antiretrovirals.

Reverse transcriptase inhibitor resistance.—Several studies examined the effects of the preceding use of specific drugs on the likelihood of developing subsequent resistance in vitro to other nRTIs. Miller et al found that the number of previously used nRTIs correlated with resistance to zalcitabine, lamivudine, and stavudine; previous use of lamivudine was associated with increased risk of stavudine resistance; and previous use of didanosine or stavudine was associated with increased risk for lamivudine resistance (Abstract 674). In an investigation of potential mechanisms by which prior nRTI use could affect the subsequent efficacy of a second drug, Sommadossi et al found that the intracellular phosphorylation to the active nucleoside triphosphate form significantly correlated with antiretroviral response to stavudine and lamivudine (Abstract 362). Moreover, long-term zidovudine treatment resulted in diminished stavudine and lamivudine phosphorylation and preceding zidovudine/stavudine was associated with decreased stavudine phosphorylation for weeks after the discontinuation of zidovudine. These two observations may partially explain the diminished efficacy of stavudine following zidovudine therapy and the zidovudine/stavudine antagonism.

Palmer et al examined the cross-resistance patterns of two multidrug resistant viral strains, one containing four reverse transcriptase inhibitor resistance mutations (75I, 77L, 116Y, 151M), and the other containing seven reverse transcriptase inhibitor resistance mutations (41L, 43N, 67N, 118I, 184V, 210W, and 215Y) (Abstract 405). The former conferred high-level phenotypic resistance to multiple inhibitors including abacavir, F-ddA, PFA foscarin, zidovudine, stavudine, didanosine, and lamivudine and partial susceptibility to PMEA and PMPA, and the latter conferred substantial resistance to abacavir, F-ddA, zidovudine, stavudine, didanosine, and lamivudine.

Protease inhibitor resistance.—Presentations of cross-resistance patterns among protease inhibitors included a study of HIV-1 clinical isolates by Hertogs et al, which defined resistance characteristics among indinavir, saquinavir, ritonavir, and nelfinavir (Abstract 395). General findings included the observation that in 77% to 95% of viral isolates with tenfold resistance to one of these four protease inhibitors, there was an association with at least a four-fold rise to the other three agents; in 62% to 79% this cross-resistance was at least tenfold. Mutations in the HIV-1 gag protease cleavage sites were also seen, most commonly an A to V substitution at the p7/p1 site, and a majority of resistant genotypes included multiple mutations (most
commonly 5). In a separate study, the appearance of these gag cleavage site substitutions did not correlate with the number of protease coding region mutations or the duration of protease inhibitor therapy (Abstract 402).

**Salvage Therapy Regimens**

**Dual Protease Inhibitor Combinations**

Ritonavir/saquinavir—Tebas et al reported the use of ritonavir/saquinavir stavudine/lamivudine following nelfinavir failure in either the Agouron 506 or 511 trials (Abstract 510). While 9 of 10 patients with limited antiretroviral therapy prior to nelfinavir responded to this salvage regimen, only 43% (3 of 7) with more extensive antiretroviral experience had reductions in plasma HIV-1 RNA levels to below 500 copies/mL (Abstract 510).

Duncombe et al reported the use of ritonavir/saquinavir combined with zidovudine/lamivudine or stavudine/lamivudine in 58 patients, 66% of whom were protease inhibitor-experienced (50% saquinavir- and 14% ritonavir-experienced) (Abstract 390). From a median plasma HIV-1 RNA of 4.49 log and a CD4 cell count of 191/μL, HIV-1 plasma viremia was decreased by a median of 1.98 log; 49% of subjects to below 400 copies/mL. In this study, neither protease inhibitor nor nRTI pretreatment correlated with virologic response. A third ritonavir/saquinavir dual nRTI salvage study presented by Cassano et al enrolled 43 patients in whom single protease inhibitor-based triple drug therapy had failed (Abstract 423). After 9 months of follow-up, patients in whom saquinavir and ritonavir or indinavir had failed reduced their plasma HIV-1 RNA levels by 1 and 1.5 log copies/mL, respectively. Respective CD4+ cell increases were 100 and 50/μL.

Response to ritonavir/saquinavir salvage therapy appears to be dependent on several factors. In the study by Tebas et al, higher plasma HIV-1 RNA levels at the time of the regimen change were associated with treatment failure. The presence of specific resistance genotypes (e.g., the L90M mutation in the protease gene) was not predictive of treatment failure, although there was a trend toward an association with lamivudine resistance. In contrast, a virologic analysis of ACTG 333 showed that an HIV-1 protease residue 10 mutation predicted subsequent failure to indinavir in patients previously treated with saquinavir hard gelatin capsule (Abstract 511).

A related retrospective analysis presented by Gallant et al suggested that treatment with ritonavir/saquinavir and two different nRTIs, after a loss of viral suppression with either indinavir or nelfinavir, was more likely to succeed if the new regimen was initiated when plasma viral loads were relatively low (Abstract 427). Responding patients (ie, subjects with plasma HIV-1 RNA levels <400 copies/mL after 16 weeks of therapy) had a mean viral load of 1.2562 copies/mL compared with 33,367 copies/mL in non-responders. The importance of changing the accompanying nRTI regimen concurrently with the protease inhibitor was demonstrated in a study presented by Rozenbaum et al in which the nRTI switch correlated with a 3.5-fold greater likelihood of achieving a plasma HIV-1 RNA level below 500 copies/mL after 10 months of therapy (Abstract 420). Bodsworth et al similarly demonstrated a virologic benefit to changing or adding to the accompanying nRTI regimen (Abstract 396).

**Protease Inhibitor/NNRTI Combinations**

Indinavir/nevirapine combinations.— Several reports of using indinavir/nevirapine in antiretroviral-experienced populations were presented. In patients with a median CD4+ cell count and plasma HIV-1 RNA level of 30/μL and 5.16 log copies/mL, respectively, who had failed or were intolerant to nRTI therapy, a regimen consisting of indinavir/nevirapine/lamivudine diminished the plasma HIV-1 RNA level to below 400 and to below 40 copies/mL in 45% and 32% of the patients, respectively, after 1 year of therapy (Abstract 429a). Murphy et al reported on 36 subjects who had been rolled over from the amprenavir monotherapy arm of ACTG 347. A combination of nevirapine/indinavir/ stavudine/lamivudine reduced plasma viremia to below 400 copies/mL in 32 of 36 of these individuals (Abstract 512). A third study by Lawrence et al used indinavir/nevirapine and two nRTIs for patients with virologic failure of saquinavir and/or nelfinavir (Abstract 422). At enrollment, the median plasma HIV-1 RNA level was 4.22 log. The combination of indinavir/nevirapine yielded a modest 0.9 log reduction in plasma HIV-1 RNA level in this patient population.

Nelfinavir/nevirapine-based combinations.— Similar to the modest and unsustained virologic responses seen with indinavir/nevirapine salvage therapy described above, Gerard et al reported that nelfinavir/nevirapine combined with foscarnet for the initial three weeks, while resulting in a 2.64 log reduction in plasma HIV-1 RNA levels at week 3, was unable to maintain viral suppression past week 8 in heavily pretreated patients (Abstract 424). A second small study using a 6-drug regimen consisting of nelfinavir/nevirapine/saquinavir/lamivudine/stavudine/didanosine in 12 patients with extensive protease and reverse transcriptase inhibitor experience, but who were nelfinavir/nevirapine-naive, preliminarily reported that at 12 weeks, 9 of the 12 patients decreased their plasma HIV-1 RNA
levels to below 400 copies/mL from a median of 64,000 copies/mL. (Abstract 426). The durability, tolerability, and safety of regimens like this need to be determined.

**Antiretroviral Strategies**

**Induction-Maintenance**

Two studies were reported that demonstrated the failure of 3- to 6-month induction periods combined with a dual nRTI protease inhibitor/nRTI, or protease inhibitor monotherapy maintenance regimen. ACTG 343, presented by Havlir et al, was a trial that employed indinavir/zidovudine/lamivudine induction followed by randomization to one of three maintenance regimens if plasma HIV-1 RNA levels were reduced to below 200 copies/mL at weeks 16, 20, and 24: the same 3-drug regimen; indinavir monotherapy; or zidovudine/lamivudine (LB16). Subjects had no protease inhibitor or lamivudine experience prior to induction therapy and had median baseline CD4+ cell counts between 437 and 463 cells/μL and plasma HIV-1 RNA levels between 17,000 and 22,000 copies/mL at the time of randomization to the maintenance regimens. Using the primary study endpoint of virologic failure defined by two consecutive plasma HIV-1 RNA levels greater than 200 copies/mL, the 3-drug maintenance regimen was substantially more effective than either indinavir monotherapy or the dual nRTI arms (3%, 23%, and 23%, respectively). Predictors of virologic failure in the zidovudine-lamivudine arm included more than 6 months of prior zidovudine use and the presence of the zidovudine-associated 215 resistance mutation. Indinavir monotherapy maintenance versus the 3-drug regimen carried a sevenfold increased relative risk for failure. A greater increase in CD4+ cell count in response to induction was associated with a 1.4-fold higher relative per 100 CD4+ cell rise risk, possibly reflective of a larger HIV-infectable cellular pool in the setting of inadequate viral suppression on maintenance therapy.

In the TRILEGE (ANRS 072) trial, the same induction regimen was used in antiretroviral naive patients with a mean baseline CD4+ cell count and plasma HIV-1 RNA level of 363/μL and 4.48 log, respectively (LB15). After 3 months of induction, subjects with plasma viral levels below 500 copies/mL were randomized to either continued indinavir/zidovudine/lamivudine, zidovudine/lamivudine, or indinavir/zidovudine maintenance. The primary study endpoint was virologic failure as defined by a resumption in measurable (>500 copies/mL) HIV-1 viremia. Six months after randomization, patients who were maintained on 3-drugs were significantly less likely to fail relative to either dual drug arms (10%, 38%, and 24%, respectively). Further validation of induction-maintenance strategies will be dependent upon studies utilizing more prolonged durations of induction and/or more potent maintenance regimens.

**Conclusions**

Studies reported at the 5th Conference on Retroviruses and Opportunistic Infections taken together form the most comprehensive summary to date of the state-of-the-art in antiretroviral chemotherapy. The principle of combining maximal regimen potency with close virologic monitoring was reinforced and the increasing number of potentially effective combinations was highlighted. Simultaneously, the shortcomings of the current therapeutic armamentarium were detailed and the spotlight placed on areas in which future research efforts must be focused. Most importantly, the overall message was one of continued progress in the field and cautious optimism for the future.

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372. Analysis of Long-term Virologic Data


381. Indinavir (IDV) in Combination with ZDV and 3TC in zidovudine-experienced patients with CD4 cell count <=50 cells/mm^3. - 60 Week Followup. J. E. HIRSCH* for the protocol 039 (indinavir) study group. A. MIEBOHM, S. RAWLINS and R. LEAV. ITT. Massachusetts General Hospital, Merck Research Laboratories.

380. Randomized Comparative Outcome Trial of Indinavir (I) and Rinovir (R) in Protease Inhibitors (PI) naïve HIV Patients (p) with CD4 below 100 cells/ul. N. CLUMECK*, B. COLEBUNDERS, R. VANDERCAM, K. KABEYA, P. CASANO, B. SOMMERELS, S. DE WIT & PICASSO Trial Group, Belgium.

379. Open Label Pilot Studies to Assess the Safety and Efficacy of bid Dosing Regimens of VIRACEPT® (nelfinavir) in HIV Infected Patients, M. SENSI, R. ELIO, C. PARTHING, J. CURRERI, C. LINQUIST, B. RICHARDSON, M. BECKER, North Broward Hospital District, Ft. Lauderdale, FL; Continuity Care Center, Washington, DC; AIDS Healthcare Foundation, L.A., CA; LACUSC Medical Center, L.A., CA; Marin County Specialty Clinic, Greenbrae, CA; Agouron Pharmaceuticals, Inc., La Jolla, CA.

378b. First Comparative Study of Saquinavir Soft Gel Capsules vs Indinavir as part of Three Drug Therapy Regimen (CHEESE). J.C. BORLEIFFS* on behalf of the CHEESE Study Team. University Hospital, Department of Internal Medicine, Utrecht, Netherlands.

378a. Combivir™, A Fixed Formulation of Lamivudine (3TC) 150 mg and Zidovudine (ZDV) 300 mg, Given BID Plus a Protease Inhibitor (PI) Compared to 3TC 150 mg BID and ZDV 200 mg TID Plus a PL EROK #, YETZER E., POERTZ D, RUANE P, BECKER S.


375. Antiviral Activity and Acceptance of Two Different Triple Combinations: D4T + Indinavir + 3TC vs D4T + Indinavir + DID. N. VILLALBA, M. GOMEZ-CANO, E. CASAS, A. MAS, V. SORIANO and J. GONZALEZ-LAZOZ. Service of Infectious Diseases, Instituto de Salud Carlos III & Hospital Principe de Asturias, Alcalá de Henares, Madrid, Spain.


389. Treatment with Ritonavir/Saquinavir Versus Ritonavir/Saquinavir/ Stavudine. B. CISOL*, R. COLEBUNDERS, F. VAN WANZEBLE, M. VAN DER ENDE, P. KOOPMANS, F. PORTGIESR, R. HOETELMANS, A. JAPOUR, P. WARD, P. DE WOLF and S. DANNER, on behalf of the Prometheus Study Group. AMC/NATEC, Amsterdam, The Netherlands (NL); Inst. For Tropical Medicine, Antwerp, Belgium (BY); University Hospital (UH), Gent; B. UH, Rotterdam; NL; UH, Nijmegen, NL; Slotervaart Hospital, Amsterdam, NL; Abbots Labs, Chicago, USA; Roche Welwyn, UK.

390. Durability of Quadruple Antiretroviral Therapy including Ritonavir and Saquinavir in Patients with Advanced HIV-1 Disease. C. DUNCOMBE*, G. KAUFMANN, A. BEVERIDGE, J. CHUAH, A. CARR, P. CUNNINGHAM, D.A. COOPER. National Centre for HIV Epidemiology and Clinical Research, Holdsworth House Practice, Grosvenor Street Clinic, Gold Coast Sexual Health Clinic, St Vincent's Hospital, Sydney, Australia.


392. Virologic, Immunologic and Histologic Responses to a 4-Drug Combination Therapy in Antiretroviral Naïve, HIV Infected Persons. MA POLIS*, L. SCHRADER, C. YODER, J. MIKAN, G. KELLY, J. METCALF, J. KOVACS, R.
406a. Mutations Selected In HIV Plasma RNA During 141W94 Therapy. DB PASQUALE
M. MURPHY R, GULICK R,
SMEATON L, SOMMADASSI J-F,
DEGRUTTOLA V, CALIENDO A,
KURITZKES D, SUTTON L, SAVARA
A, D’AGUILA R* for the ACTG 347
Boston, MA.; Northwestern U, Chicago,
IL; NYU, NY, NY; UAB, Birmingham,
AL; UCHSC, Denver, CO.

407. Multiple Symmetrical Lipomatosis
Associated with Protease Inhibitor Therapy. HENGEL RL*, GRARY JAM,
VUCHEITICH MA, SWARTZ AS,
BRACHMAN PS, WATTS NB, LENNOX
JL. Emory University and Grady Health
Systems, Atlanta, GA.

408. "Protease-Paunch" in HIV+ Persons
Receiving Protease Inhibitor Therapy: Incidence, Risks and Endoscopic
Evaluation. ROSENBERG HP*, MULLER
J, SEPKOWITZ K, GIORDANO
ME. Cornell University Medical College,
NY.

409. Buffalo Hump in HIV-infected Patients
On Antiretroviral Therapy. JC LO*, K MULLIGAN, VW TAI, H ALOREN, M
SCHAMBELAN. UCSF-San Francisco
General Hospital, San Francisco, CA.

410. A Syndrome of Peripheral Lipodystrophy
(LO), Hyperlipidemia and Insulin
Resistance due to HIV Protease Inhibitors
(PI’s). A. CARR*, K. SAMARAS, S.
BURTON, J. FREUND, D. A. CHISHOLM,
D.A. COOPER. St. Vincent’s Hospital,
Garvan Institute of Medical Research,
National Centre in HIV Epidemiology
and Clinical Research, Sydney, Australia.

411. Development of a Cervical Fat Pad
Following Treatment with HIV-1 Protease
Inhibitors. VL ROTH, JB. ANGEL*, S.
KRACKVIK, Ottawa General Hospital,
Ottawa, Canada.

412. Abnormal Fat Distribution in AIDS
Patients Following Protease Inhibitor
Therapy: FDA Summary. M. MANN*, I.
PIAZZA-HEPP, E. KOLLER, C. GIBERT.
FDA, Rockville, MD, VAMC, Washington,
DC.

413. Increased Intr-Abdominal Fat Deposits in
Patients on Indinavir. K. MILLER*, E.
JONES, J. YANOFSKI, R. SHANKAR, I.
FEUERSTEIN, and J. FALLOON, Warren
G. Magnuson Clinical Center & National
Institute of Allergy and Infectious
Diseases, National Institutes of Health,
Bethesda MD.

414. Evidence of Unique Metabolic
Effects of Protease Inhibitors. K MULLIGAN*, VW TAI, H ALOREN, DN CHERNOFF, JC
LO, M SCHAMBELAN. University of
California San Francisco - SF General
Hospital, San Francisco, CA; Chiron
Diagnostics & Chiron Corporation,
Emeryville CA.

415. Diabetes and Hyperglycemia in Patients
Receiving Protease Inhibitors. JC KERU-
LY*, RE CHAISSON, RD MOORE. Johns
Hopkins University, Baltimore, MD.

416. Diabetes and Use of Protease Inhibitors.
BJ DONG*, C. GRUTA, J. LEGG,
K.BALANO, RHLGOLDSCMITH, San
Francisco General Hospital, San Francisco,
CA.

417. Acute Hepatitis in Aids Patients During
Ritonavir Treatment. ARRBAS JJ*,
GONZALEZ-GARCIA J, IBANEZ C,
RUZ, PENA JM, ESTEBAN C, FRIAS
J, VAZQUEZ J. Hospital "La Paz" and

418. Increased risk of Indinavir Neoplasms in
Women. M SARCETTI, A PETTER, K
LEHTTA, P KONIG, R. ZANGERLE*,
University of Innsbruck, Innsbruck, Austria.

420. Predictors and Incidence of Failure in 500
Advanced Stage HIV Patients Treated with
Indinavir. ROZENBAUM W*, ADDA N,
WIRBEL, E. HADACEK, B. SCHNEIDER
V, COSTAGLIOLO D. Hospital Rothschild,
INSERM SC4, ISARS, Paris, France

422. Salvage Therapy with Indinavir plus
Nevirapine in Patients Previously Treated
with Two Other Protease Inhibitors and
Multiple Reverse Transcriptase Inhibitors.
J. LAWRENCE*, J. SCAPPIRO, M.
WINTERS, J. MONTOYA, A. ZOLOPA,
R PESSAO, D. WINSLOW, T.C. MERIG-
AN Stanford University, Stanford, CA.
Ageron Pharmaceuticals, La Jolla, CA.

423. Combined Quaddraple Therapy with
Ritonavir-Saquinavir (RTV-SQV) +
Nucloides in Patients (p) who Failed in
Triple Therapy with RTV, SQV or
Indinavir (IDV), B. CASSANO, P. HER-
MANS, B. SOMMEREUNS, S. DE WIT,
K. KABEYA, E. O’DOHERTY, N.
CLUMECK*, C.I.H. Saint-Pierre,
Brussels - Belgium.

424. Salvage Anti HIV Triple Therapy with
Foscarnet (F) in Combination with
Ritonavir (NEL) and Nevirapine (NEV) in
Heavily Pretreated Patients (p). G. GE-
ARD*, S. DE WIT, S. SPRECHER, F.
DE COCK, Y. VAN LAETHEM, P. HER-
MANS, M.-C. PAYEN, K. KABEYA, P.
CASSANO, N. CLUMECK. C.I.H. Saint-
Pierre and Institut Pasteur, Brussels,
Belgium.

426. Salvage Therapy using Six Drugs in
Heavily Pretreated Patients. WORKMAN,
C*, MUSSER, R, SULLIVAN, J. 75
463. Factors Associated With Survival in HIV-infected Patients With Progressive Multifocal Leukoencephalopathy. MS DWORKIN, D CT WAN, DL HANSON, JL JONES.CDC, Atlanta, GA.


466. Fatal Progression Multifocal Leukoencephalopathy (PML) Despite Highly Active Antiretroviral Therapy (HAART), Inferon-alpha 2b (IFN-a-2b), and Tefnine T. PI PIERRON*, AD NGUYEN, M. REIF. Albany Medical College, Albany, NY.

467. Predictors of Virologic and Clinical Responses to Indinavir (IDV)+ZDV+3TC or ZDV+3TC. M DEBROT*, M HUGH- ES, M FISCHL, J. GRIMES, R BOSCH, K SQUIBES, AND HAMMER for the ACTG 320 Study Team. NIAID, Bethesda, MD.

468. Virologic responses to a Ritonavir/Saquinavir-containing regimen in Patients who have previously failed Nelfinavir. P TESARI*, E. KANE, M KLEBERT, J SIMPSON, W. POWER, K. HENRY. Wash Univ, St. Louis, MO. Univ of Minnesota, Minneapolis MN, Regions Hospital, St Paul, MN.


470. 141W94 with or without Zidovudine/3TC in Patients with an Prior Protease Inhibitor or 37C Therapy-37C. MURPHY R*, DEGRUTTOLA V, GULICK R, D'AQUILA R, BON J, SOMMADIOSI JF, SMEATON L, CURRIER J, TUNG R, KURITZKES D for the ACTG 347 team, Northwestern U*, Chicago, IL; Harvard U, Boston, MA; NYU, New York, NY; UNC, Chapel Hill, NC; UAB, Birmingham, AL; USC, Los Angeles, CA; Vermont, Cambridge, MA; UCHS, Denver, CO.

515. Presence of an Inducible HIV-1 Latent Reservoir During Highly Active Antiretroviral Therapy. TAE-WOOK CHUN* AND ANTHONY S. FAUCI, Laboratory of Immuno-regulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.


520. In vivo attenuation of SIVmac239 by mutation of conserved Tyr in the TM cytoplasmic tail. JAMES A. HOXIE*, MICHAEL J. EndRIS, PATRICIA J. VANCE, BINLI TAO, MARK MARSH, PATRICIA N. FULTZ, Unv. of Pennsylvania, Phila., PA; Unv. of Alabama, Birmingham, Al; Univ College London, UK.

522. Impact of Highly Active Antiretroviral Therapy (HAART) on the Stabilization of the TCR 8 Chain Repertoire During Primary HIV Infections. HUGO SOUDEYNS*, GP RIZZARDI JF DEMAREST, A. LAZZARIN, AS FAUCI, L COREY, G. PANTALEO. CHUV, Lausanne, Switzerland. Duke University, Durham NC. San Rafiele Scientific Institute, Milan, Italy. NIAID, NIH, Bethesda MD. University of Washington, Seattle WA.

523. Rate of Production of HIV in Lymphatic Tissue Measured During the Acute and Very Early Stages of Infection Is Not Related to Duration of Infection. SCHACKER, T.W.*, GEBHARD, K., KRIEBER, J., COREY, L. and HAASE, A.T. University of MN, Mpls, MN, University of Washington, Seattle WA.


564. HIV-1 Vpr suppresses immune activation and apoptosis through regulation of nuclear factor kB. VELPANDI AVYAVOO, ARTIN MAHBOUBI, S. MAHALINGAM, R. RAMALINGAM, SAGAR KUDCHUKAR, WILLIAMS V. WILLIAMS, DOUGLAS R. GRIESEN AND DAVID B. WEINBERG*. Department of Pathology, University of Pennsylvania, Philadelphia, PA USA; La Jolla Institute of Allergy and Immunology, San Diego, CA; Roche Institute of Molecular Biology, Nutley, NJ.

565. HIV-1 Vpr Alters Potentially Bone Marrow Cell Function. JOSEPH KULKOSKY*, ALEXY LAPYEV, SUBHIRA SHETTY, ALAGARSAMY SRINIVASAN, NEAL FLOMENBERG, DARWIN-PROCKOP and ROGER J. POMERANTZ. Dorrance Hamilton Laboratories, Center for Human Virology, Thomas Jefferson University, Philadelphia Pa. and Center for Gene Therapy, Allegheny University of the Health Sciences, Philadelphia, PA.

587. Dynamics of T Lymphocytes in Acute HIV Infection Before and After Treatment. LITTLE S.A., HAVLIR D., RICHMAN D., MCLEAN A., SPINA C. UCSF, CA and Oxford Univ., U.K.

588. Lack of CDS8 Cell Activation and Cytotoxic T-Lymphocyte (CTL) Activity Until Discontinuation of Highly Active Antiretroviral Therapy (HAART) for Primary HIV Infection. DAAE E. BAIJ, HAUSNER MA, MACHROWICZ M, GIORGIO JV, Cedars-Shafr Medical Center, LA, CA; UCLA School of Medicine, LA, CA.


630. Antiretroviral activity and metabolism of bis (POC) PMPA, an oral bioavailable prodrug of PMPA. ARNOLD FRIDLAND*, BRIAN L. ROBBINS, RANJA V. SAINI-VAS, NORBERT BISKOPFBERGER, St.

564. Safety, Sheltering, & Synergy of Hydroxycure (fu) with did or d4t in HIV-infected Patients. J.E. GIBLIN*, F. LORI, D.R. GLOBE, D.CASCIATO. Shared Medical Research, Taranto, CA; I.R.I.G.H.T. Institute, Pavia, Italy.

565. Consistent, sustained HIV suppression without rebound by hydroxycure, did, and a protease inhibitor prevent loss of immunologic function. LORI E.*, JENSEN H., CLERICI M., LEIBERMAN I., AND LISPESZCZ J. RIGHT, S. MATTEO, Pavia, Italy, and Georgetown University, Washington, DC Jensen Praxis, Berlin, Germany, Sacco Hospital, Milan, Italy, Center for Blood Research, Boston, MA.


567. Improvement in CD4 Cell Diversity during 7-Month Trial of Hydroxycure in Combination with did or d4t and d4t. J.E. GIBLIN*, F. LORI, D.R. GLOBE, D. CASCIATO, Shared Medical Research, Taranto, CA; I.R.I.G.H.T. Institute, Pavia, Italy.


567. Correlates of Resistance to Individual Nucleoside Drugs in Patients Who Have Never Taken Them. V. MILLER, AN PHILLIPS*, K. HERTOOG, M-P BETHUNE, P. PAULES, S STASZEWSKI. Goethe Universitat, Frankfurt, Germany, Vic, Antwerp, Belgium, Royal Free School Of Medicine, London, UK.

567. Antiretroviral Susceptibilities of HIV-1 RT Recombinant Viruses Derived from AIDS.

680. The M184V Substitution in Reverse Transcriptase Increases Sensitivity of Both HIV-1 and SIV to PMPA. MARK A. WAINBERG, YUDONG QUAN, HORACIO SALOMON, and JULIE CHERRINGTON. McGill AIDS Centre/Jewish General Hospital, Montreal, Quebec, Canada and Gilead Sciences, Foster City, CA, USA.


687. Susceptibility of Clinical HIV-1 Isolates to 3TC. MELLORS JW, HERTOGS KG, PIEETERS F, LANIER R, MILLER V, GRAHAM N, LARKER B, STOFFELS P, PAUWELS R. University of Pittsburgh/VAMC, Virco Belgium/UK/USA, Glaxo Wellcome USA, University of Frankfurt, Germany, Tissoir Belgium.

690. Durability of Clinical Anti-HIV-1 Activity (60 Weeks) and Tolerability for Efavirenz (DMP 266) in Combination with Indinavir (IDV). Suspension to <1 Copy/ml (OD-Background) by Ampliseq as a Predictor of Virological Treatment Response [DMP 266-003, Cohort IV]. J. KAHN, D. MAYERS, S. RIDDLER, D. STEIN, M. BACH, D. HAVIL, N. RUIZ, D. MANION, P. FRIEDMAN, D.F. LABRIOLE, K. GORELICK, E. PAULKNER, T. SAXTON, A. GOLDBERG, G. CSAY and The DMP 266 Clinical Development Team. San Francisco General Hospital, San Francisco, CA; Natl Naval Medical Center, Bethesda, MD; Univ of Pittsburgh, Pittsburgh, PA; Albany Med Coll, Albany, NY; Bach and Godofsky, Bradenton, FL; Univ of California Treatment Center, San Diego, CA; Dapont Merck, Wilmington, DE.

692. Use of HIV-1 RNA PCR in Patients on Zidovudine (ZDV) Voice of Pneumocystis. H. DIETRICH, M. BURLE, A. WEINER, J. ROTTER, J. SIEGEL, M. GOLDBERG, A. KORS, and the DMP 266 Clinical Development Team. San Francisco General Hospital, San Francisco, CA; Natl Naval Medical Center, Bethesda, MD; Univ of Pittsburgh, Pittsburgh, PA; Albany Med Coll, Albany, NY; Bach and Godofsky, Bradenton, FL; Univ of California Treatment Center, San Diego, CA; Dapont Merck, Wilmington, DE.

694. Use of HIV-1 RNA PCR in Patients on Zidovudine (ZDV) Voice of Pneumocystis. H. DIETRICH, M. BURLE, A. WEINER, J. ROTTER, J. SIEGEL, M. GOLDBERG, A. KORS, and the DMP 266 Clinical Development Team. San Francisco General Hospital, San Francisco, CA; Natl Naval Medical Center, Bethesda, MD; Univ of Pittsburgh, Pittsburgh, PA; Albany Med Coll, Albany, NY; Bach and Godofsky, Bradenton, FL; Univ of California Treatment Center, San Diego, CA; Dapont Merck, Wilmington, DE.

706. HIV-1 Drug Susceptibilities During Treatment with Delavirdine (DLV)+ZDV, DLV+DDI, or DLV+ZDV=DDI. L DEMBETTER, B ORPITH, R BOSCH, W SCOTT, M NOKITA, E FISHER, R PILLARD, W FREIMUTH, M FISCHER, & G FREIAND for the ACTG 261/252 Study Team, NIAID, Bethesda, MD.

708. Genotypic Evidence of Local HIV Expression in the Female Genital Tract. SUBBARAO S, WRIGHT T, ELLERBROCK T, LENNOX J, HART C. CDC and Emory University, Atlanta, GA; Columbia Univ., NY, NY.


711. HIV is Readily Detectable in the Female Genital Tract of HIV- Positive Women. A. KOVACS, P. RIEHL for the DATRI 009 Study Team, USC, Los Angeles, CA, NIAID, Bethesda, MD.

715. Quantification of Circoviralgenital Uvea and Plasma HIV-1 RNA in HIV-1 Seropositive Women. CRAIG HODGKIN, GREG SPATKANOS, SONIA BRAGG, RONALD ALVAREZ, and KATHLEEN SQUIRES. University of Alabama at Birmingham, Birmingham, Alabama.

716. HIV RNA Level in the Genital Tract of Women on Antiretroviral Therapy. CU UVIN S, CALIENDO A, RUSSO R, REINERT S, FLANIGAN TP, MAYER KH, CARPENTER CCI. Brown University, Providence, RI, Harvard Medical School, Boston, MA.

717. HIV Shedding Occurs Through the Viral Infection. HART C, LENNOX J, EVANS-STRICKFADEN T, BUSCH T, SUEHLE C, CLANCY K, PRAST-PALMORE M, CONLEY L, ELLERBROCK TV. CDC and Emory University, Atlanta, GA.


728. Mycobacterium Avian Intrapulmonale (MAIs) Reversal Syndrome Set off By Highly Active Anti Retroviral Therapy (HAART). Improved Immunity Is Not Always Good...
HIGHLIGHTS OF THE 5TH RETROVIRUS CONFERENCE

but it is Better Than No Immunity. MARK H KAPLAN* North Shore University Hospital, Manhasset, N.Y.

729. Endocarditis of Disseminated Mycobacterium avium complex (MAC) in Four Patients after Twelve Months Anti-Mycobacterial therapy and Response to Highly Active Antiretroviral Therapy (HAART). J.A. ABERG*, D.M. YAJKO and M.A. JACOBSON University of California San Francisco; San Francisco General Hospital, San Francisco, CA and UCSF Center for AIDS Research


LB5. A Randomized Trial of 2 Months of Rigamun (RIF) and Pyrazinamide (PZA) Versus 12 Months of Isoniazid (INH) for the Prevention of Tuberculosis (TB) in HIV-Positive (+), PPD+ Patients (pts). F GORDIN, R CHAISSON, J MATTIS, C MILLER, L GARCIA, R HAFNER, R O'BRIEN for the CPCRA/ACTG/PAHOC/DCC Study Team, VA Medical Center, Washington, DC.

LB6. Fomiviren Safety and Efficacy in the Treatment of CMV retinitis: A Phase 3, Controlled, Multicenter Study Comparing Immediate Versus Delayed Treatment. C MUCCIOLI, DA GOLDSTEIN, DW JOHNSON, JE PEREZ, JF MORA-DUARTE, JD SHEPPARD, SE MAN- SOUR, CK CHAN, AG PALESTINE, JR GRILLONE, and JW CHANDLER*, Federal Univ. of Sao Paulo, Sao Paulo, Brazil; Univ. of IL, Chicago, IL; Univ. of CO, Denver, CO; FI LCAderli, FL; Inst. Costarricense de Invest. Clinicas, San Jose, CR; Virginia Eye Consultants, Norfok, VA; Santa Clara Valley Med. Ctr., San Jose, CA; So. Calif. Desert Retina Consultants, Palm Springs, CA; Washington, DC; and las Pharmaceuticals, Caribad, CA.


LB8. The Safety and Efficacy of Fmma Prodrug Monotherapy: Preliminary Results of a Phase II Dose-escalation Study. STEVEN G. DEBBS*, PATRICIA BARDITCH-CROVO, PAUL S. LETMAN, ANN COLLIER, SHARON SAFRIN, RBBEC-CA COLEMAN, KENNETH C. CUNDY, JAMES O. KIAN University of California San Francisco; Johns Hopkins University School of Medicine, Baltimore MD; University of Washington, Seattle WA; Gilead Sciences Inc. Foster City, CA.

LB9. Potent Antiretroviral Efficacy of Low Dose FTC, Initial Results from a Phase VII Clinical Trial. JOHN POTTAGE, MELANIE THOMPSON, JAMES KAHN, JOHN DELHANTY, BRUCE McCREDY, FRANCK ROUSSEAU*. CCCR, Chicago, IL; AIDS Research Consortium, Atlanta, GA; UCSF, San Francisco, CA; Triangle Pharmaceuticals, Durham, NC.

LB11. Drugs suppressing HIV replication and cell proliferation decrease proviral DNA to undetectable levels. LORI E. JESSON H, CLERICI M, LIEBERMAN J, SILLIANO RJ, and J. RIGHT, S. Matteo, Pavia, Italy, and Georgetown University, Washington, DC, Jesan Praxis, Berlin, Germany. Chamberϊnian, Milan, Italy. Center for Blood Research, Boston, MA; Johns Hopkins University, Baltimore, MD.


LB15. Results of TRIEGLE Trial, a Comparison of Three Maintenance Regimens for HIV Infected Adults Receiving Induction Therapy with Zidovudine (ZDV), Lamivudine (3TC), and Indinavir (IDV). F RAPF*, G. PIALOUX, F. BRUN-VEZINET, J. GASTAUT, P. DELLAMONICA, J.F. DELBRAISSE, Y. MIERFREDY, P. FLANDRE, J.P. ABOUFLEUR, for the ANRS 072 Study Group; Univ. Hosp., Nantes; Paris; Marseille; Nice; and INSERM SC10, Villejuif, France.


L3. Immunopathogenesis of primary immunodeficiency virus infections. NORMAN L. LETTIN, LING SHEN, KEITH A. Riemann, CHRISTOPHER MILLER, ZHENG WEI CHEN, JOERIN E. SCHMITZ, and MARCELO J. KURANDA. Harvard Medical School. Beth Israel Deaconess Medical Center, Boston, MA; California Regional Primate Research Center, Davis, CA.

L4. HIV infection: the body fights back. BRUCE D. WALKER. Massachusetts General Hosp., Charlestown.

L5. T-cell immune reconstitution in HIV negative hosts. CRYSTAL L. MACKALL, National Cancer Institute, Bethesda, MD.

S3. The effect of polymorphisms in the regulatory regions of the CCR5 promoter on HIV-1 vertical transmission and on disease progression in infected children. JOHN P. MOORE*, LEONHOS KOSTRIKIS, DAVID D. HO. Aaron Diamond AIDS Research Center, New York, NY.


S8. Epstein-Barr virus and lymphoma in patients with HIV. RICHARD F. AMBINDER.


S24. The cellular export pathway that transports HIV-1 Rev from the nucleus to the cytoplasm. KARSTEN WEIS*, KATRIN STADE, CHRISTINE GUTHRIE, and CHARLEEN FORD-RAY. UCSF, Dept. of Biochemistry & Biophysics, San Francisco, CA.


S27. PTEPb kinase: an essential HIV Tat cellular cofactor. HELENA MANECHO, GARY LEE, JOAN TOMASSINI, DARIO HAZUDA, and OSVALDO FLORISI. Department of Biology, Tularik Inc., South San Francisco, CA. Department of Antiviral Research, Merck & Co., West Point, PA.

S39. Analysis of HIV-1 Vif protein function. MICHAEL H. MALIM, JAMES H.M. SIMON, RON A.M. FOUCHIER, and NATHAN C. GADDIS. Howard Hughes Medical Institute and Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA.

S40. The many tricks Nef plays on the cell. DIDIER TRONO, YEN-LIANG CHIN, VINCENT PIQUET, JUAN LAMA, ARAM MANGASARIAN, and JEN-KUEI WANG. Department of genetics and Microbiology, University of Geneva, Switzerland.

S41. A role for Nef in lymphocyte activation. RONALD C. DESSROSJERS. Harvard Univ., Southborough, MA.

S42. HIV-1 Vpr and the cell cycle. WEI CHUN GOH, MARK E. ROGEL, C. MATTHEW KINSEY, SCOTT P. MICHAEL, PATRICIA N. FULTZ, BEATRICE H. KAHN, and MICHAEL EMERMAN*.

S45a. Genetic variants in chemokine receptor and chemokine genes that regulate progression to AIDS. STEPHEN J. O'BRIEN, MICHAEL DEAN, MARY CARRINGTON, MICHAEL SMITH, CHERYL WINKLER, J. CLAIBORNE STEPHENS, WILLIAM S. MODI. ALIVE, HGDS, MACS, MHCS, and SFCC AIDS cohort studies.
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