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Summaries of the Sixth Conference on Retroviruses and Opportunistic Infections: Part II

CONFERENCE COVERAGE

Note: *The following summaries represent a selection of papers from those presented at the 6th Conference on Retroviruses and Opportunistic Infections held on Jan. 31-Feb. 4, 1999, in Chicago, IL. It is important to recognize that some of these summaries are extracted only from the published abstract and it is possible that some of the material presented at the conference may have differed. The abstracts and posters, as well as other information presented at the conference, are available on the internet at www.retroconference.org. —Stan Deresinski, MD, FACP*

HIV Infection

Combination Therapy, Pharmacokinetics, and Controlled Dosing

The results of two studies indicate that antiretroviral dosing must be approached with caution in patients with hepatic disease. Efavirenz Cmax was significantly lower in patients with chronic liver disease when compared to matched controls in a single-dose study. The areas under the curve (AUC) did not differ between the two groups, but there was a trend toward a longer half-life in liver disease patients. The investigators interpret these findings (decreased Cmax but no change in AUC) as possibly being explained by reduced absorption offset by reduced rate of elimination. (*Abstract 367.*)

Administration of nelfinavir to patients with severe liver disease resulted in prolonged half-life and significantly reduced concentrations of the active M8 metabolite. Two patients with reduced clearance had dose reduction to 500 mg bid and 250 mg tid to achieve desired nelfinavir ranges. There was wide variability in pharmaco-

kinetics in patients with liver disease. (*Abstract 369.*)

Relative to historical results with indinavir administered 800 mg q 8 h, administration of 800 mg q 12 h together with either 100 mg, 200 mg, or 400 mg of ritonavir resulted in the following increases in indinavir pharmacokinetic characteristics: Cmax: 30-50%; Cmin: 15- to 35-fold; 24-hour AUC: three-fold. The increase in indinavir levels was modestly greater when taken with 200 mg or 400 mg ritonavir than with 100 mg. Taking the drugs with food did not significantly affect indinavir pharmacokinetics except for a delay in time to peak drug concentration. The half-life of ritonavir was prolonged and its Cmin increased, while the effect of food on ritonavir was eliminated. (*Abstract 362.*)

Separately, administration of indinavir (IDV) 800 mg bid together with ritonavir 100 mg bid resulted in decreased indinavir Cmax but increased Cmin when compared to levels achieved with indinavir 800 mg q 8 h alone. (*Abstract 363.*) No cases of nephrolithiasis were noted among 57 patients receiving indinavir and ritonavir (each 400 mg bid) during a total of 2412 weeks on therapy. (*Abstract 677.*)

Coadministration of indinavir 1200 mg and nelfinavir 1250 mg, each q 12 h, resulted in indinavir Cmax, AUC24, and Cmin comparable to those achieved when indinavir 800 mg q 8 h is administered alone. There was no significant effect on nelfinavir pharmacokinetics. (*Abstract 364.*)

ACTG 359 is an example of the potentially complex, sometimes unanticipated consequences of the practice of polypharmacy. This six-armed trial compared saquinavir/ritonavir and saquinavir/nelfinavir together with delavirdine, adefovir, or delavirdine/adefovir. The resultant pharmacokinetic interactions were complex. Adefovir appeared to decrease delavirdine AUC, possibly in turn accounting for an observed decrease in saquinavir AUC in patients receiving those three drugs. Delavirdine appeared to increase the AUC of saquinavir, ritonavir, and nelfinavir. (*Abstract 365.*)

Coadministration of methadone resulted in a mean decrease in AUC of ddI of 41% and of d4T of 27%, possibly as a result of decreased bioavailability. There was no apparent effect on methadone exposure. (*Abstract 371.*)

Coadministration of nevirapine resulted in withdrawal symptoms in patients on stable doses of methadone as the result of increased metabolism of the latter. (*Abstract 372.*)

The AUC of meperidine decreased by a mean of 67% in patients also receiving ritonavir, while the mean normeperidine AUC increased 47%. Ritonavir pharmacokinetics did not appear to be affected. The investigators conclude that, contrary to previous recommendations, meperidine administration is not contraindicated during ritonavir therapy. (*Abstract 373.*)

Coadministration of nevirapine resulted in increased clearance of clarithomycin reflected in a 46% decrease in its Cmin, a 29.5% decrease in its AUC, and a 20.8% decrease in its Cmax. There was, however, a 57.7% increase in the AUC and a 62.1% increase in Cmax of the active metabolite, 14-OH-clarithromycin. The nevirapine Cmin, Cmax, and AUC each increased by approximately 25%. These results suggest that no adjustment in clarithromycin dosage is required in patients receiving nevirapine. (*Abstract 374.*)

Treatment-naïve patients were randomized to receive either "concentration-controlled" (CC) or standard therapy with AZT, 3TC, and indinavir. Dose adjustments were made in the former group based upon individual pharmacokinetic analyses performed at weeks 2 and 30. Dose modifications in the CC group for AZT were required for 56% of patients, for 3TC in 11%, and for indinavir in 78% to achieve target levels. The administered doses ranged from 600-900 mg/d for AZT, 300-450 mg/d for 3TC, and 2400-3200 mg/d for indinavir. Pharmacokinetic parameters were stable within individuals over six months. (*Abstract 368.*)

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Which of the following is correct?

a. Coadministration of methadone is associated with increased AUC of ddI (didanosine).
b. Coadministration of methadone is associated with increased AUC of d4T (stavudine).
c. Coadministration of nevirapine may result in narcotic withdrawal symptoms in patients receiving methadone-maintenance therapy.
d. Clarithromycin dosage should be reduced by one-half in patients receiving nevirapine.

Treatment of AR-naïve Patients

Antiretroviral(AR)-naïve patients received bid d4T with either daily or bid ddi/nevirapine with equivalent results. (*Abstract 628.*) The VIRGO trial also demonstrated efficacy of similar regimen. (*Abstract 632.*) Efavirenz containing regimens are effective in patients with baseline plasma HIV RNA of more than 100,000 copies/mL and remain so for as long as 84 weeks. (*Abstracts 382, 383.*)

AR-naïve patients were randomized to receive either ritonavir/saquinavir/d4T or indinavir/d4T/3TC. At 12 months, 70% of the former and 83% of the latter (P = 0.67) had plasma HIV RNA less than 400 copies/mL. (*Abstract 630.*)

PI and NNRTI-naïve patients were randomized to receive saquinavir(sgc) 1200 mg tid or 1600 mg bid, each in combination with two new NRTIs, or saquinavir(sgc) 1600 mg bid plus nelfinavir 1250 mg bid plus one new NRTI. Results at 32 weeks indicate that all four regimens were equally successful. Thus, bid treatment regimens containing saquinavir or saquinavir plus nelfinavir appear to be effective as well as convenient. (*Abstract 390.*)

Treatment-naïve patients, initially randomized to receive either AZT/3TC or d4T/3TC, had indinavir added to their regimens after 12 weeks. Excellent sustained virological responses were observed, with no differences between the groups; 83.3% of patients had viral loads less than 50 copies at 48 weeks and 66.7% were still negative at 72 weeks. There was, however, a significant (P < 0.0001) difference in CD4 rise between those who received d4T/3TC with indinavir (mean increase of 330 cells/mm^3) and those who received AZT/3TC with their PI (mean increase of 150 cells/mm^3). (*Abstract 635.*) This finding was not observed in a separate study, however, in which treatment-naïve patients were randomized to receive indinavir with either AZT/3TC, d4T/3TC, or d4T/ddI. There was no significant difference between groups with regard to either viral load or CD4 response. (*Abstract 633.*)

Follow-up of 30 patients (PI and 3TC naïve, but AZT experienced) receiving indinavir/AZT/3TC found that 20 (67%) had plasma HIV RNA less than 50 copies/mL for up to 148 weeks of therapy. Thirty-nine percent had at least one episode of nephrolithiasis and 19% had evidence of lipodystrophy. (*Abstract 388.*)

AR-naïve patients with CD4 count more than 200 cells/mL and plasma HIV RNA more than 500 copies/mL were randomized to receive d4T/ddI/3TC, d4T/ddI/NVP, or d4T/ddI/IDV. Preliminary "as-treated" analysis of results in 102 patients completing 24 weeks of therapy found that 76%, 81%, and 81%, respectively, had achieved a plasma HIV RNA less than 50 copies/mL. (*Abstract 18.*)

One hundred seventy-three therapy-naïve patients were randomized to receive either 3TC/ZDV with or without abacavir (ABC). Seventy-five percent of those receiving all three drugs achieved plasma HIV RNA less than 400 copies/mL at 16 weeks while only 35% of those receiving the two-drug regimen did so. After 16 weeks, all patients were given the opportunity to include ABC in their regimens; addition of ABC at that time resulted in a subsequent one $\log_{10}$ decrease in viral load that was sustained to 48 weeks. (*Abstract 19.*)

Five hundred sixty-two antiretroviral therapy(ART)-naïve patients with CD4+ count more than 100 cells/mm^3 and plasma HIV RNA more than 10,000 copies/mL were randomized to receive either ABC/3TC/ZDV or IDV/3TC/ZDV. There was no significant difference in CD4 count rise or reduction in viral load between the two treatment groups after 24 weeks. (*Abstract 20.*)

One hundred fifty-seven PI-naïve patients were randomized to receive: 1) saquinavir(sgc) 1200 mg tid plus 2 NRTIs; 2) nelfinavir 750 mg tid plus 2 NRTIs; 3) saquinavir(sgc) 800 mg tid plus nelfinavir 750 mg tid plus 2 NRTs; or 4) saquinavir(sgc) 800 mg tid plus nelfinavir 750 mg tid. By an intent-to-treat analysis with missing values considered failures after 72 weeks of therapy, 51% of NRTI-experienced patients receiving the four-drug regimen had plasma HIV RNA less than 50 copies/mL, compared to 22-35% in the two-drug arms. The time to relapse was shorter in the three-drug arms than in the four-drug arm. Quadruple therapy appeared superior to triple therapy in patients with baseline viral load more than 4.8 copies/mL than in those with lower viral load. These results suggest that quadruple therapy containing two PIs may be preferable in treating NRTI-experienced patients and those with high baseline viral loads. (*Abstract 389.*)

Yet, another study demonstrated that a strategy of induction followed by maintenance using fewer drugs during the latter phase is ineffective. (*Abstract 627.*)

Twenty PI-naïve patients received ritonavir 400 mg q 12 h plus nelfinavir given in a dose of either 500 mg or

750 mg q 12 h. Both regimens were equally effective. (*Abstract 393.*)

Discordant results between viral load and CD4 response were observed in 35.6% of a large cohort of previously treated patients in response to HAART. Patients who had had a CD4+ T cell increase of more than 50 cells/mm^3 had a favorable prognosis after a median of 13 months, regardless of whether they had had a virological response, defined as a decrease in viral load of at least one log_{10}. Patients with a virological, but not a CD4, response had an intermediate prognosis. (*Abstract 169.*)

Which of the following is *not* correct?

a. A strategy of induction therapy with HAART followed by maintenance with a reduced number of drugs is ineffective.
b. In patients with discordant CD4 and viral load responses in response to HAART, a virological response provides a more favorable prognosis than a CD4 response.
c. The addition of abacavir alone to stable background therapy resulted in improved virological responses.
d. The presence of virus with only one or two mutations associated with NRTI resistance is not associated with a reduced virological response to addition of abacavir alone to stable background.

Treatment of NRTI-Experienced Patients

One hundred ninety-five PI-naïve patients with prior extensive NRTI treatment experience in the context of ACTG 175 and subsequent rollover trials were randomized to nelfinavir, efavirenz, or nelfinavir/efavirenz—each with one or two new NRTIs. By weeks 40-48, the plasma HIV RNA was less than 500 copies/mL in, respectively, 35%, 60%, and 74%. Thus, both the nelfinavir/efavirenz and efavirenz arms were superior to the nelfinavir arm (P = 0.001). Similar increases in CD4 counts were observed in all arms. (*Abstract 489.*)

In contrast to previous reports, there was no difference in either d4TTP formation or the ratio of d4TTP to dTTP between AZT-naïve and experienced patients. Thus, prior AZT therapy does not appear to impair subsequent intracellular phosphorylation of d4T. (*Abstract 487.*)

Intensification

Several studies demonstrated that the addition of abacavir (ABC) to stable background therapy resulted in improved virological responses. (*Abstracts 377, 378.*) In the course of one of several clinical trials, 88 patients had ABC added to their baseline regimens; their duration of prior NRTI therapy was three months to many years. The antiviral efficacy of ABC was similar whether baseline virus was wild type or had one or two mutations associated with NRTI resistance. The presence of three or more mutations was, however, associated with a reduced response. Only 6% of these heavily pretreated patients had phenotypic resistance (> 8-fold wild type) to ABC. (*Abstract 134.*)

In a study of saquinavir together with two NRTIs, suppression of plasma HIV RNA to less than 400 copies/mL by 12 weeks or less than 50 copies/mL by 24 weeks predicted a durable response persisting to at least 72 weeks. (*Abstract 165.*) Patients not achieving these benchmarks may be considered candidates for therapy intensification.

Patients with CD4 counts less than 101 cells/mm^3 or 101-200 cells/mm^3 after a nadir of less than 50 cells/mm^3 were randomized to receive either adefovir dipivoxil or placebo (each plus L-carnitine) in addition to their stable background therapy. There was no evidence that the addition of adefovir improved survival or affected viral loads. The incidence of proximal tubular disorder in patients on adefovir for 12 months was 22%. (*Abstract 491.*) Proximal tubular disorder was observed to resolve in 79% with a median time to resolution of 15 weeks. (*Abstract 678.*)

Salvage Therapy

Thirty-seven patients who had failed multiple drug regimens were given six or more antiretroviral drugs (mega-HAART) and were followed for a mean of eight months. Significant decreases in viral load were seen and maintained for the period of follow-up in many patients; 10 patients achieved and maintained a plasma HIV RNA level of less than 500 copies/mL. (*Abstract 130.*)

Forty-nine patients with plasma HIV RNA more than 100,000 copies/mL, despite protease inhibitor-based therapy, were given hyodroxyurea/efavirenz/ddI/ritonavir/indinavir plus up to two NRTIs. Therapy was generally tolerated. Nine (60%) of 15 subjects who reached 24 weeks of therapy had plasma HIV RNA less than 400 copies/mL. (*Abstract 400.*)

ABC/amprenavir(APV)/EFV was administered to heavily pretreated patients failing their current regimens. Although most baseline viral isolates contained more than four RTIs and more than five PI resistance-associated mutations, 55% were phenotypically susceptible to APV, 42% to ABC, and 75% to EFV. Fifty-six percent of patients with baseline susceptibility to more than one of the drugs achieved a plasma HIV RNA less than 2.6 log_{10} copies/mL. Incomplete virological response or viral rebound by week 16 was primarily associated with the development of genotypic and phenotypic resistance to efavirenz. (*Abstract 133.*)

Twenty-four patients who had failed a nelfinavir containing regimen were treated with a regimen con-

taining ritonavir/saquinavir. All 24 patients had decreases in plasma HIV RNA to less than 500 copies/mL and this response was sustained for 24 weeks of therapy in 71%. Using the "last observation carried forward" method, 58.3% remained undetectable after a median follow-up of 61 weeks. The presence of D30N, N88D, or M36I mutations was not predictive of failure. (*Abstract 392*.)

Ten patients who had failed multiple therapies and who had defined patterns of mutational drug resistance were given, after a one-month "washout" off therapy, EFV/ddI/adefovir/hydroyxurea. One patient had "full viral suppression" (< 20 copies/mL) that persisted for the 16 weeks on therapy; that patient had baseline RT mutations at positions 41, 184, and 215. (*Abstract 135*.)

Sixty-four patients with plasma HIV RNA more than 500 copies/mL while on a PI-containing regimen were given a new combination regimen containing nelfinavir. Most were NNRTI-naïve. One-third achieved a viral load less than 500 copies/mL. An increasing number of mutations at key PI- and RT-resistance sites was associated with a trend toward decreased response to the new regimen. Patients with none or only one mutation at protease codons 48, 82, 84, or 90 and who had four or fewer mutations at key RT codons were most likely to respond to therapy. (*Abstract 136*.)

Ninety-four NNRTI-naïve with plasma HIV RNA more than 500 copies/mL while receiving indinavir/AZT or d4T/3TC were randomized to receive either: abacavir/efavirenz/adefovir/nelfinavir; abacavir/-efavirenz/adefovir; new NRTIs (not abacavir)/-efavirenz/adefovir/nelfinavir; or new NRTIs (not abacavir/efavirenz/adefovir). Good responses were obtained in the three nelfinavir-containing arms. (*Abstract 490*.)

In a five-arm trial, patients received hydoxyurea alone at one of two doses (1000 mg q/d or 1500 mg q/d), ddI alone (200 mg bid), and ddI plus each of the two doses of hydroxyurea. Patients assigned ddI alone had hydroxyurea added after 12 weeks. Hydroxyurea alone had no antiretroviral effect but was synergistic with ddI, however, the addition of hydroxyurea to existing ddI monotherapy had no significant effect. A dose of 1500 mg of hydroxyurea daily was more toxic than the lower dose. (*Abstract 402*.)

Which of the following is correct?

a. Hydroxyurea administration to patients already receiving ddI monotherapy was associated with a significantly improved virological response.
b. A synergistic virological response was observed with simultaneous initiation of hydroxyurea and ddI administration.
c. No significant difference in toxicity was observed in patients receiving a total daily dose of either 1000 mg or 1500 mg of hydroxyurea.
d. Resurgence of plasma virus in patients receiving indinavir is invariably associated with detectable resistance-associated mutations to this drug.

Antiretroviral Targeting of the CNS

Virus may evolve independently in cerebrospinal fluid and plasma in patients with AIDS dementia complex. This could lead to compartmentalized drug failure. (*Abstract 297*.) Such differences in drug susceptibility between virus isolates from different anatomic sites does not necessarily imply the existence of "drug sanctuaries;" modeling of HIV populations indicates that this process may be a stochastic one. (*Abstract 307*.)

Treatment with ritonavir/saquinavir was associated with persistence of HIV RNA in cerebrospinal fluid in the majority, while the addition of d4T was associated with undetectable virus in this compartment. Cerebrospinal fluid levels of the PIs were below the level of quantitation in 21 of 25 patients. (*Abstract 403*.)

Eleven antiretroviral-naïve patients were started on AZT/3TC/nevirapine/indinavir. The mean plasma and CSF viral loads at baseline were, respectively, 244,613 and 167,319 copies/mL. Although still detectable in CSF at two months, at six months all CSF and nine plasma samples had HIV RNA less than 50 copies/mL. Indinavir was detectable in all but one CSF sample at a concentration of 27-228 ng/mL and was stable throughout the eight-hour dosing interval (the IC95 is 18-70 ng/mL). Nelfinavir could not be detected in CSF in two patients who substituted this drug for indinavir. Thus, it often requires more than two months of effective HAART to make HIV RNA undetectable in CSF. (*Abstract 404*.)

A separate study found a median level of indinavir in CSF of 89 nM in patients receiving this drug (range, 26-294) with a median CSF:plasma ratio of 0.16 (range, 0-2.28). These concentrations exceed the IC95 of wild-type strains. (*Abstract 407*.)

Three antiretroviral treatment-naïve patients underwent frequent CSF sampling during the first seven days of therapy with d4T/3TC/nelfinavir. Discordant decay of HIV RNA was found in comparing CSF to plasma, suggesting the presence of a distinct CSF compartment of viral replication. The concentration of d4T in CSF, sampled at 11 time points in each patient, was 39% ± 7% of plasma levels. Nelfinavir and 3TC concentrations were not reported. (*Abstract 405*.)

CSF and blood were repeatedly sampled in six subjects receiving nevirapine 200 mg bid. Nevirapine concentration ranged from 336 to 2781 and from 889 to 11840 ng/mL in CSF and plasma, respectively. The CSF:plasma AUC ratio was 0.287; the nevirapine concentration in each sample was above the reported IC50

of susceptible strains. (*Abstract 406.*)

A post-mortem study found that brain levels of HIV RNA did not correlate with the degree of neurological disease or the number of antiretroviral-resistance mutations. (*Abstract 298.*) However, improvement in neuropsychiatric performance eight weeks after starting HAART is strongly associated with virological response as measured in CSF. (*Abstract 408.*)

Which of the following is correct?

a. Treatment with ritonavir and saquinavir alone is associated with rapid eradication of detectable HIV RNA from cerebrospinal fluid (CSF).
b. The addition of d4T to ritonavir and saquinavir does not accelerate the eradication of detectable HIV RNA from CSF.
c. Indinavir is commonly detected in CSF in concentrations exceeding the IC95 of wild-type virus in patients receiving this drug.
d. CSF concentrations of ritonavir and saquinavir in patients receiving these drugs are readily detectable and well in excess of the IC95s of wild-type virus.

Viral Fitness

One puzzling observation has been the maintenance, or even an increase in CD4+ T-cell count in the face of ongoing viral replication. One potential explanation is reduced viral fitness, an observation first made in association with development of the M184V 3TC-associated resistance mutation, a mutation associated with decreased replicative capacity of HIV-1. It is now clear that, as expected, other mutations may affect viral fitness. Thus, ddI-resistant strains with either Leu74Val or Met184Val RT mutations exhibit decreased processivity of RT, probably accounting for decreased fitness in these strains. (*Abstract 592.*)

This phenomenon has also been observed in association with PI therapy. It has previously been demonstrated that mutations in the protease gene may lead to impaired proteolytic activity of HIV protease and that PI-resistant mutants may exhibit reduced fitness in vitro. In order to determine whether this is also true in vivo, human thymus implants in the SCID-hu Thy/Liv mouse were infected with either wild type or protease inhibitor-resistant mutants of HIV-1. While the wild type virus replicated to high levels and caused T-cell depletion, the virus containing PI gene mutations exhibited highly limited replication without associated T-cell depletion. While other explanations, such as changes in immunologic control are possible, the results of this study are consistent with impaired in vivo viral fitness. (*Abstract 4.*)

Reduced viral fitness may be seen in association with virological relapse in patients receiving HAART. In one cohort, the median loss of viral fitness associated with failure of PI therapy was 27.5% and was strongly correlated with PI resistance but not with plasma HIV RNA levels. Fitness diminution did, however, correlate with increase in CD4 count 3-6 months after viral sampling (P = 0.006). (*Abstract 331.*) Also consistent with reduced viral fitness, many patients failing PI therapy have a sustained rise in CD4 count, albeit at a slower rate than non-failures. This phenomenon is dependent upon the absolute level of viremia, indicating a persistent adverse effect of viremia on the rate of CD4 increase. (*Abstract 494.*)

On the other hand, HIV may preserve its replicative capacity in the face of PI therapy by the development of mutations at the site of protease cleavage of viral polyprotein. In a study of 70 protease inhibitor experienced patients, the presence of *gag* cleavage site mutations was strongly associated with low CD4 count and, in a logistic regression model, was the only independent predictor of this finding. (*Abstract 128.*)

In addition to specific site mutations, viral recombination may affect viral fitness. Longitudinal analysis of a patient infected with two highly divergent subtype B strains of an R5 HIV-1 demonstrated a complex series of recombination events. Eventually, one recombinant variant displaced all other viral populations and remained relatively homogenous until the patient's death. Thus, recombination together with selection is "a potent mechanism used by the virus to rescue variants of declining fitness within the host." (*Abstract 90.*)

It is possible that changes in viral fitness may at least partially explain the puzzling finding of virological resurgence during continued therapy without evidence of in vitro resistance. For instance, sequencing of RT and protease genes of virus from patients who had virological failure while receiving AZT/3TC/indinavir or indinavir/efavirenz found that, while more than 70% had RT resistance-associated mutations, less than 25% had virus with PI resistance-associated mutations. (*Abstract 492.*)

In a trial in which treatment-naïve patients received indinavir plus one or more nucleoside analogs and/or a nucleotide analog (adefovir), sequencing of the RT gene from virus obtained during therapy failed to reveal resistance mutations in the majority of the 18% with detectable plasma HIV RNA. (*Abstract 112.*) Similarly, virus from 26 patients, some previously reported, had virological failure while receiving indinavir unassociated with genotypic or phenotypic indinavir resistance. Susceptibility to indinavir persisted for a mean of six months in 17 patients failing triple therapy and in nine patients failing indinavir monotherapy. Mean serum indinavir levels did not differ

between treatment failures and controls. Although indinavir resistance was absent, the RT M184V mutation and associated phenotypic resistance to 3TC was observed in 14 of the 17 patients failing triple therapy. The investigators suggest these data may be explained by a fitness advantage of the rebounding virus compared to early protease mutants emerging in the presence of indinavir. (*Abstract LB12.*)

Immune Based and Gene Therapy

Therapeutic Vaccination. The administration of whole HIV-1 immunogen (REMUNE) to HIV-1 infected patients improved in vitro responses to HIV-1 antigens. (*Abstract 346.*) The administration of a DNA plasmid vaccine containing HIV-1 *env/rev* and *gag/pol* genes to patients receiving HAART was associated with the development of in vitro responses to the administered antigens. (*Abstract 347.*)

T-Cell Infusion. HLA-matched T cells of four HIV-negative twins were repeatedly administered to the HIV-infected brother after initiation of HAART. There was evidence of gradual CD4+ T-cell repopulation. Whether this was due to HAART or to adoptive T-cell transfer was, however, unclear. (*Abstract 360.*) Infusion of expanded autologous HIV *gag*-specific CD8+ T cells was associated with retention of their cytolytic activity in vivo, their accumulation adjacent to HIV-infected cells within lymph nodes, and transient reduction of the number of circulating productively infected CD4+ T cells. (*Abstract 26.*)

Immune Modulators. Cyclically administered subcutaneous rhIL-2 in individual doses of 1.5-7.5 million IU to antiretroviral-treated patients with CD4+ T-cell counts of more than 350 cells/mm^3 were tolerated and resulted in significant increases in CD4+ T-cell counts, particularly at the highest doses. There was no significant change in viral load. (*Abstract 354.*) Cyclical administration of nine MIU daily in cycles in patients receiving HAART gave similar results. (*Abstract 356.*) In another trial of similarly administered rhIL-2 with doses of three MIU bid or greater, given in cycles, resulted in a mean increase in CD4+ count of 698 cells/mm^3. (*Abstract 355.*)

Seventy-eight patients were randomized to receive antiretroviral therapy alone or with rhIL-2, 7.5 MIU bid subcutaneously, administered for up to six cycles. CD4 counts increased 115% in those with baseline CD4+ T-cell counts of 200-300 cells/mm^3, 101% in those with 301-400, and 110% in those with 401-500 CD4+ T cells/mm^3 at baseline. There was a nonsignificant trend toward a larger proportion of patients with viral loads below the level of detection in those receiving rhIL-2. (*Abstract 357.*) This, as well as the inability to detect latently infected CD4+ T cells in several patients given HAART plus rhIL-2, suggests a possible antiviral effect of this cytokine. (*Abstract 496.*)

Six of 11 intensively studied patients had a transient increase in plasma HIV RNA of at least 0.5 $\log_{10}$ during at least one cycle of rhIL-2 administration. Quasispecies analyses of plasma RNA and cellular proviral DNA indicated that this rise is the result of amplification of preexisting replicating viral species rather than activation of silent reservoirs of proviral DNA in peripheral blood mononuclear cells. (*Abstract 358.*)

T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40 ligand (CD40L) interactions. CD40L inhibits SIVmac239 replication. (*Abstract 544.*) WF10, an IV formulation of tetrachlorodecaoxygen, improves macrophage function in vitro. Administration to HIV-infected patients was associated with improved phagocytosis index. There was no effect on plasma HIV RNA concentration. (*Abstract 359.*)

Gene Therapy. Cells transfected with an SV40 expression vector delivering a single chain variable fragment (SFv) directed at viral integrase were partly protected from productive HIV infection. (*Abstract 619.*)

Six patients were infused, without myelosuppression, with autologous CD34+ peripheral blood hematopoietic stem cells that had been transduced with an anti-TAT ribozyme. Vector-marked cells were detectable in the bone marrow and peripheral blood granulocytes, T cells and monocytes at weeks 4 and 12 in four patients studied to date. No significant changes in viral load or CD4 count were observed. (*Abstract 17.*)

CD4+ lymphocytes obtained from four HIV-negative twins and transduced with a hammerhead ribozyme targeted to the HVI-1 tat gene were repeatedly infused into HIV-infected siblings. Gene-marked cells were detected for as long as 10 months post-infusion indicating persistent survival of the transduced cells in vivo. CD4+ T-cell counts remained stable and viral load remained low. (*Abstract 361.*)

New Antiretrovirals Under Investigation

Protease Inhibitors (PI). Recombinant strains containing V82A, G48V/V82A, V82A(F)/L90M, or I84V/L90M, while resistant to other PIs, remained susceptible to the new PI, AG1776. (*Abstract 11.*)

ABT-378 is a potent PI with limited bioavailability when given alone but has excellent levels when administered with a low dose of the CYP3A4 inhibitor, ritonavir. Antiretroviral therapy-naïve patients were given d4T and 3TC plus ABT-378 (200-400 mg bid) and ritonavir (100-200 mg bid). Therapy was well tolerated and more

than 90% of patients had plasma HIV RNA less than 400 copies/mL after 24 weeks. (*Abstract 15.*)

BMS-232632 is an azapeptide HIV-1 PI with in vitro potency and, in Phase I studies, 60% oral bioavailability with a mean terminal half-life of 2.9-6.5 hours. (*Abstracts 603, 604.*)

Nucleoside Analog Reverse Transcriptase Inhibitors (NRTI). Lodenosine (F-ddA), a purine RT inhibitor, is active against M151R containing strains of HIV-1 that are resistant to multiple NRTIs. A Phase I trial in heavily pretreated patients demonstrated modest antiviral effect at the doses administered. (*Abstract 380.*) Eighty-one antiretroviral-naïve patients were randomized to receive either 3TC or one of three doses of FTC for 12 days. Patients receiving the highest dose of the latter (200 mg q/d) had a somewhat better virological response than did those receiving 3TC in the standard dose of 150 mg bid. (*Abstract 16.*) Both enantiomers of BCH-10652 (dOTC), a racemic mixture of a thioocytidine nucleoside analog, have potent in vitro activity and, in Phase I trials, have a plasma half-life of 9.7-18.2 hours and is well tolerated. (*Abstracts 595, 596.*)

Nonnucleoside Analog Reverse Transcriptase Inhibitors (NNRTI). The NNRTI, AG1549, remained active against recombinant constructs resistant to other NNRTIs; significant reductions in susceptibility to AG1549 were seen only in strains containing two or more NNRTI substitutions. (*Abstract 12.*)

DMP 961 and DMP 963 are three- to eight-fold more active against K103N-containing virus than efavirenz and each has a plasma half-life of 20-76 hours in the chimpanzee. (*Abstract 13.*)

The quinoxaline class NNRTI, GW420867X, has potent in vitro activity against HIV-1 and, in Phase I trials, has a plasma half-life of approximately 50 hours and is well tolerated. (*Abstracts 599-601.*)

(+)-Calanolide A is an NNRTI derived from a tree found in the rainforest of Sarawak, Malaysia, *Calaphyllum lanigerum*. Phase I studies indicate it is well absorbed after oral administration and has a T1/2 of 15-30 hours. Another tree from Sarawak, *Calaphyllum teysmannii* var. *inophylloide*, is the source of (-)-calanolide B, which like (+)-calanolide A, has potent in vitro activity against HIV-1. (*Abstracts 606, 602.*)

Inhibitors of Viral Binding, Fusion, or Cell Entry. PRO 542, a fusion protein consisting of a portion of human IgG2 with the Fv segment replaced with the V1 and V2 domains of the CD4 molecule, is active in vitro against HIV-1 and was well tolerated in a Phase I trial. (*Abstract 618.*)

AR177 is an oligonucleotide that inhibits viral entry into target cells. T140 binds to CXCR-4 inhibiting viral infection with anIC90 of 2.9 nM. (*Abstract 608.*) AMD-3100 also blocks CXCR-4; its median terminal half-life after IV administration to normal volunteers is 2.8 hours; white blood cell count elevation was noted in all recipients. (*Abstract 610.*) The addition of methionine to the N terminus of SDF1-beta (Met-SDF1), a natural ligand of CXCR-4, inhibits viral infectivity in vitro. (*Abstract 615.*)

T-20, a 36-amino acid synthetic peptide is a potent inhibitor of HIV-1 fusion and cell entry with demonstrated antiviral activity in humans. However, it may select for mutations in the envelope region involved in its binding and inhibition of gp41-mediated membrane fusion. (*Abstract 611.*) In contrast to the activity of other antiretrovirals, a paradoxical transient increase in plasma viral load occurs in the first 24 hours after administration of T-20, followed by a rapid decline. (*Abstract 612.*)

T-20 was administered in various doses to 78 patients on no or continuing stable antiretroviral therapy for 28 days. There was a dose-related suppression of plasma HIV RNA levels and the drug was well tolerated. (*Abstract LB13.*) "Peptide-2" is a fusion inhibitor related to T-20 that has activity in vitro against some T-20 resistant strains. (*Abstract 617.*)

FP-21399, a low molecular weight fusion inhibitor, was administered intravenously in escalating doses for at least 48 weeks to 19 patients on stable or no antiretroviral therapy. While there was a modest increase in CD4 count, there was no significant change in viral load. Some patients reported blue urine and blue injection sites. (*Abstract 614.*)

Frameshift Alteration. HIV-1 uses programmed-1 ribosomal frameshifting in the synthesis of the *gag-pol* gene product. Since an imbalance in the *gag* to *gag-pol* ratio can interfere with viral replication and assembly, and since eukaryotes do not use similar frameshifting, this is an attractive potential therapeutic target. Sparsomycin, a frameshift stimulator, is a potent inhibitor of HIV replication. (*Abstract 621.*) ❖

In Future Issues:

Outpatient Parenteral Antibiotic Therapy