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Perspectives

Original Contribution

Special Contribution

About This Issue

We include in this issue of *Topics in* HIV *Medicine* 2 reviews of current clinical issues in HIV medicine: a summary of a lecture by Stuart C. Ray, MD, at our CME course in San Francisco, on the science and management of HIV and hepatitis C virus coinfection, and Dr Constance A. Benson's review of key new data on treatment interruption and investigational new antiretroviral drugs, given at our course in New York this fall.

In an adaptation of a keynote lecture delivered at a leadership conference in New York City in June, Michael H. Merson, MD, makes the case for the importance and efficacy of global HIV prevention programs. The meeting, *Curtailing the* HIV *Epidemic: The Power of Prevention Leadership Forum*, was hosted by the Henry J. Kaiser Family Foundation, the Ford Foundation, and the Bill and Melinda Gates Foundation.

This issue also includes an update, from the International AIDS Society–USA Drug Resistance Mutations Group, of drug resistance mutations that occur in HIV-1. This December 2001 update reflects new research on drug resistance mutations published or presented this summer and fall, and represents the ongoing efforts of the group to provide a current listing of mutations to HIV clinicians and scientists. The update was also published online at www.iasusa.org.

This issue concludes with our annual end-of-the-year appreciation of the audience members, funders, faculty, staff, consultants, and vendors whose contributions to the International AIDS Society–USA in 2001 made our educational programs possible.

The International AIDS Society–USA fall 2001 course in New York, *Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management,* was supported through unrestricted educational grants from **Merck US Human Health, Abbott Laboratories, Agouron Pharmaceuticals, Inc., DuPont Pharmaceuticals Co.,** and **Gilead Sciences, Inc.**

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Announcements

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Key Updates from Recent Research Conferences: Structured Treatment Interruption, Intermittent Treatment Strategies, and New Drugs in Development

Recent information from studies of structured treatment interruption, intermittent treatment strategies, and new antiretroviral drugs currently in development were discussed at the International AIDS Society–USA course in New York by Constance A. Benson, MD. Dr Benson's discussion of treatment interruption was limited to the application of this approach in patients with acute HIV-1 infection and in patients with chronic HIV-1 infection and suppression of viral replication during potent antiretroviral therapy. Most of the studies reviewed by Dr Benson were (or will be) presented at 4 conferences in 2001: the 8th Conference on Retroviruses and Opportunistic Infections, in February; the 5th International Workshop on HIV Drug Resistance and Treatment Strategies, in June; the 1st IAS Conference on HIV Pathogenesis and Treatment, in July; and the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, in December.

In the context of this discussion, a subtle distinction is made between structured treatment interruption (STI) and structured intermittent treatment (SIT). STI has generally referred to 1 or more periods of interruption of potent antiretroviral therapy after a period of full viral suppression, with the principal goal being stimulation of HIV-1-specific immune responses that might subsequently improve control of viral replication in the absence of therapy. SIT has generally been applied to a treatment strategy of cyclic periods of potent antiretroviral therapy coupled with defined periods of no therapy, with the principal goal being maintenance of immune function and viral suppression with a reduction in overall drug exposure that might subsequently limit adverse effects or toxicities. However, in several of the studies addressed below this distinction is blurred.

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Structured Treatment Interruption

Acute Infection

The rationale for STI in acute HIV-1 infection is based on the hypothesis that repeated cycles of fully suppressive antiretroviral therapy followed by cycles of treatment interruption may preserve or stimulate HIV-1-specific CD4+ T helper cell responses and strong, broadly directed HIV-1-specific CD8+ cytolytic T cell (CTL) responses, and that these responses might result in immunologic control of viral replication in the absence of treatment. In one of the initial investigations of this approach (Rosenberg et al, *Nature*, 2000), 8 of 16 patients treated with potent antiretroviral therapy for acute symptomatic infection and identified prior to seroconversion underwent cyclic STI. Therapy was started within 2 to 34 days of symptom onset and continued for 358 to 1081 days, and plasma HIV-1 RNA levels were consistently less than 50 copies/mL before the first STI.

After the first STI, plasma HIV-1 RNA rebounded at a median of 17 days in all 8 patients; in 3, plasma HIV-1 RNA subsequently decreased to less than 5000 copies/mL despite no further therapy. After restarting therapy, a second STI in 5 patients was associated with a lower viral rebound followed by a decrease in plasma HIV-1 RNA to less than 5000 copies/mL. Of these 5, 1 patient had a gradual increase to 17,000 plasma HIV-1 RNA copies/mL after approximately 6 months, 2 remained off therapy with less than 300 HIV-1 RNA copies/mL after approximately 6 months, and 2 elected to restart treatment with plasma HIV-1 RNA levels of 4000 to 10,000 copies/mL. Thus, 5 of 8 patients remained off treatment with control of plasma HIV-1 RNA. Characterization of immune responses showed that Gag-specific T helper and CTL responses increased significantly, with a broadened epitope response compared with baseline and decreased clonal diversity compared with that in control subjects.

A number of investigators have followed these initial observations with additional studies addressing similar hypotheses in the setting of acute HIV-1 infection. An example of one such investigation is a European study, details of which are to be presented at the 2001 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Miro and colleagues enrolled 12 patients identified within 90 days of acute infection who have plasma HIV-1 RNA levels of less than 20 copies/mL after at least 1 year of treatment with stavudine/lamivudine/indinavir. The subjects underwent STI consisting of 4 cycles of 2-month interruptions and 2- to 4-month treatment periods, with or without interleukin-2 treatment during the first 2 interruptions. The study is specifically evaluating control of plasma HIV-1 RNA after the fourth STI cycle, the nature of HIV-1-specific T cell responses, and the potential for genotypic changes associated with resistance.

Overall, the proof of concept for STI in acute infection appears to have been established in a small number of patients in a select few uncontrolled studies. Questions remain regarding the generalizability of these preliminary data. Specifically, it remains unknown whether the control of virus replication in this setting is the result of early potent treatment followed by cyclic

treatment interruption, or which patients and what proportion of patients might respond to this approach. In practice, it is difficult to identify acutely infected individuals, and experience in early disease research programs has shown that many patients treated during acute infection discontinue therapy due to difficulties in adhering to complex drug regimens or to adverse effects of treatment before protocols can be completed. In addition, the longer-term consequences of the approach are not known, including durability and long-term clinical significance of response to STI, potential for viral resistance, and potential for repopulation of viral reservoirs.

One of the principal concerns raised about treatment interruption, either in the setting of acute or chronic HIV-1 infection, is the potential for repopulation of latent viral reservoirs. One recently reported study suggests that reservoir reseeding may not occur in all patients. In this study (Tremblay et al, *Antiviral Ther,* 2001), HIV-1 quantitative cultures of serial dilutions of CD8+-depleted peripheral blood mononuclear cells (PBMCs) were performed, and levels of infectious virus and clonal genotypic characteristics of *env* and *pol* genes were compared at time points before and after STI. The investigators observed no increase in infectious virus concentrations in PBMCs, and a greater than 3-fold decrease in this reservoir was reported in 4 of 7 patients. However, virus evolution on genotypic analysis was observed in some patients, signaling ongoing viral replication despite the overall reduction in viral load.

Chronic HIV-1 Infection with Suppression of Viral Replication

The rationale for STI in chronic infection, in which viral replication as measured in peripheral blood is suppressed through antiretroviral therapy, is similarly based on the hypothesis that cycles of STI after prolonged suppression of viral replication might stimulate HIV-1-specific CD4+ T helper cell and CTL responses that are absent or diminished in chronic infection. These responses might result in improved immunologic control of infection after treatment discontinuation, permitting reduction of drug exposure and treatment-associated complications and improved quality of life.

The Swiss-Spanish Intermittent Therapy Trial has provided data on such an approach in the largest patient group evaluated to date. In this study (Fagard et al, 8th CROI, 2001), 128 patients with plasma HIV-1 RNA levels of less than 50 copies/mL and CD4+ cell counts above 300/µL on potent antiretroviral therapy underwent 4 cycles of 2 weeks off treatment/8 weeks on treatment. Treatment was stopped at 40 weeks and patients were followed up off therapy for up to 52 additional weeks. Therapy could be restarted if plasma HIV-1 RNA levels increased above 5000 copies/mL. The study end points were percentages of patients with less than 5000 HIV-1 RNA copies/mL of plasma and CD4+ cell counts above 400/µL at weeks 52 to 96. Viral rebound to more than 5000 copies/mL occurred in 76% of patients after the first STI and in 79% after the fourth, with the median levels of rebound being similar. No significant change in CD4+ cell count was seen. A total of 24 patients (19%) failed to have plasma HIV-1 RNA levels resuppressed to less than 50 copies/mL with resumption of treatment. Failure to achieve resuppression was associated with high baseline plasma HIV-1 RNA level, low CD4+ cell count, and high level of rebound during treatment interruption; 1 patient developed viral resistance that required treatment modification.

Overall, 9 (17%) of 54 patients who completed the protocol through at least week 52 had plasma HIV-1 RNA levels of less than 5000 copies/mL at week 52, with 3 (6%) of 54 having plasma HIV-1 RNA levels of less than 50 copies/mL; the ability to maintain suppression of plasma HIV-1 RNA off therapy was associated with improved HIV-1-specific CD4+ T helper cell and CTL responses. Updated results of this trial at future conferences are likely to provide additional insights into the durability of the HIV-1-specific immune responses and their relationship to control of viral replication, albeit in this small proportion of patients.

Other recent studies have attempted to identify alternative treatment interruption strategies that might improve upon the proportion of chronically infected patients able to maintain viral suppression in the absence of therapy. In one recently published case-control study (Garcia et al, AIDS, 2001), 10 patients with chronic HIV-1 infection, plasma HIV-1 RNA levels above 5000 copies/mL, and CD4+ cell counts above 500/µL underwent 1 year of potent antiretroviral therapy followed by 3 STI cycles of 24 weeks on treatment/4 weeks off treatment and 1 year off treatment. Virologic and immunologic outcomes were compared with those in 20 matched treatment-naive controls observed for 1 year without treatment. After 1 year off treatment, cases had a decrease in plasma HIV-1 RNA level of 0.54 $\log_{10}$ versus an increase of 0.24 $\log_{10}$ in controls and a CD4+ cell count increase of 145/µL versus a decrease of 91/µL, respectively (both statistically significant differences). HIV-1-specific CTL responses were observed in 7 of 9 cases versus 1 of 7 controls, and HIV-1-specific CD4+ T helper cell responses were observed in 5 of 9 cases versus 0 of 7 controls (the latter a statistically significant difference). Six of 9 cases had a plasma HIV-1 RNA set point lower than the baseline level compared with 0 of 7 controls; in 4 of the 6 cases, plasma HIV-1 RNA levels of less than 5000 copies/mL were maintained off therapy.

In a small randomized study (Ruiz et al, AIDS, 2001), patients with plasma HIV-1 RNA levels suppressed to less than 50 copies/mL for at least 2 years on potent therapy underwent 3 cycles of STI (n=12) or received continuous therapy (n=14). Plasma virus doubling time was prolonged after the second and third STI, with calculated viral reproductive rate decreasing by 13%, and time to achievement of plasma HIV-1 RNA levels below 50 copies/mL was reduced after each interruption. Increases in HIV-1-specific CTL responses were observed in 4 of 12 STI patients versus 0 of 14 continuous treatment patients, and HIV-1 p24 lymphoproliferative responses were observed in 5 of 12 STI patients versus none of the continuous treatment patients.

Another recent study assessed the effects of adding hydroxyurea to treatment in patients undergoing STI (Garcia et al, *Antiviral Ther,* 2001). Twenty patients with chronic HIV-1 infection who had received lamivudine/stavudine/indinavir for 52 weeks and had plasma HIV-1 RNA

levels of less than 20 copies/mL for more than 32 weeks were randomized to continued treatment with the regimen or addition of hydroxyurea. They underwent 5 STI cycles of 2 weeks off treatment/2 months on treatment, with hydroxyurea being stopped during the first 3 interruptions and maintained during the last two. A total of 16 patients were followed up for at least 6 months off treatment after the fifth cycle. Viral rebound occurred in all patients. However, mean viral doubling time increased from the first to fifth cycles, from 2.08 to 6.2 days in the hydroxyurea group and from 3.3 to 5.6 days in the group not receiving hydroxyurea. The peak of viral rebound was lower when hydroxyurea treatment was continued through the interruption period than when hydroxyurea was also interrupted. HIV-1-specific CTL responses increased between the first and last interruptions in 5 of 6 patients receiving hydroxyurea and in 5 of 8 in the group not receiving hydroxyurea. After a median follow-up of 40 weeks after the final STI cycle, plasma HIV-1 RNA of less than 5000 copies/mL was seen in 5 of 7 patients receiving hydroxyurea and in 3 of 9 patients on the initial regimen.

The emergence of resistance to the antiretroviral drugs used in regimens being evaluated in patients undergoing treatment interruptions remains a concern, both in the setting of acute and chronic HIV-1 infection. Several ongoing studies are attempting to evaluate the magnitude and consequences of emergence of viral resistance during treatment interruption. One example is a recent study in 12 chronically infected patients with plasma HIV-1 RNA levels below 50 copies/mL for more than 2 years on potent therapy, who subsequently underwent 3 STIs. The study showed that the lamivudine-associated resistance mutation M184V was present in 2 patients after the second or third STI, each of whom had received lamivudine prior to starting potent therapy (Martinez-Picado et al, *Antiviral Ther*, 2001). A stepwise increase in the frequency of M184V mutations was observed over the 3 STIs, with the eventual emergence of the mutant strain as the dominant viral population in peripheral blood, although the M184V mutant strain demonstrated reduced replication capacity. However, the M184V mutant was not detected in clones from the proviral DNA of PBMCs. The investigators interpreted their findings to suggest that STI in chronic infection may select for resistant virus that was present as a minority population prior to STI.

Intermittent Treatment Strategies

Among a number of novel treatment strategies being investigated to reduce the adverse effects or complications associated with long-term antiretroviral therapy are those focusing on intermittent treatment designed to reduce overall drug exposure. Preliminary data from 2 studies of intermittent therapy have recently been reported by Dybul and colleagues (8th CROI, 2001). In these studies, patients with plasma HIV-1 RNA levels below 500 copies/mL for 3 to 6 months and below 50 copies/mL at entry, with CD4+ cell counts above 300/µL, were enrolled. In the first of these, a pilot study (Dybul et al, 8th CROI, 2001), patients were treated with stavudine/lamivudine/indinavir on a 7 days on/7 days off schedule for 24 months. Of the 24 patients subsequently reported, all had plasma HIV-1 RNA levels below the limits of detection at the end of 24 months, with no decrease in CD4+ cell counts observed. In an update of these data, Fauci (1st IAS Conf, 2001) reported significant decreases in triglyceride, total, and low-density lipoprotein cholesterol levels observed after 2 to 4 months of intermittent therapy cycles. Follow-up continues in this study, and a randomized comparative trial is planned.

In the second study (Dybul et al, 8th CROI, 2001), 70 patients were randomized to continuous potent therapy versus cycles of 8 weeks on/4 weeks off therapy. Viral rebound occurred in all patients receiving cyclic treatment during each interruption, with approximately 20% failing to have resuppression to less than 50 copies/mL when treatment was restarted. Patients in the cyclic treatment arm also exhibited a substantial decline in CD4+ cell count during the first interruption, with the count stabilizing thereafter. In an update of this study, Fauci (1st IAS Conf, 2001) reported that M184V or K103N mutations were observed after 4 to 6 cycles in 4 of 8 patients receiving zidovudine/lamivudine/efavirenz. This latter finding led the investigators to exclude from participation in this study patients receiving this or other nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens as their antiretroviral treatment. Evaluation of lipid levels and other metabolic abnormalities is ongoing.

Recent changes in the recommendations for when to initiate antiretroviral therapy have provided the opportunity to examine effects of treatment discontinuation in patients who began therapy earlier in their disease course (eg, at plasma HIV-1 RNA levels <30,000-50,000 copies/mL or CD4+ cell counts >500/µL) than currently is recommended. A prospective observational study to be presented by Parish and colleagues at the 2001 ICAAC is examining differences in plasma HIV-1 RNA levels, CD4+ cell count, and resistance after treatment discontinuation among 39 patients with no history of CD4+ cell count below 200 cells/µL or opportunistic infection, according to whether the patients met current guidelines for starting treatment when potent therapy was initiated.

In conclusion, cyclic treatment interruptions after a period of prolonged suppression of viral replication with potent antiretroviral therapy appears to be a promising strategy to improve immunologic control of virus replication in a proportion of patients with acute HIV-1 infection. In those who develop or maintain HIV-1-specific immune responses, short-term control of viral replication in the absence of treatment may be demonstrated. This approach to therapy in the setting of chronic HIV-1 infection has resulted in more mixed responses, with only a minority of patients demonstrating consistent improvement in HIV-1-specific CD4+ T helper cell or CTL responses and control of viral replication in the absence of therapy. While improvement in some metabolic parameters has been reported with intermittent therapy, presumably related to the decrease in overall drug exposure, this improvement appears to be offset by the potential for substantial declines in CD4+ cell count (a median decline of 16 cells/month in one study [Tebas et al, 1st IAS Conf, 2001]), the development or recurrence of opportunistic infections,

and emergence of antiretroviral drug resistance in some patients during periods of treatment interruption.

New Drugs in Development

A number of new antiretrovirals are currently in development. Several of these have been in development for some time and data regarding their activity have been extensively reviewed in previous publications, and these will not be discussed further here. These include extended-release stavudine, emtricitabine, and amdoxovir (DAPD) among the nucleoside reverse transcriptase inhibitors (nRTIs), the entry inhibitor pentafuside (T-20), and the nucleotide reverse transcriptase inhibitor tenofovir (recently approved by the US Food and Drug Administration).

Newer nRTIs in development include DPC-817 and BCH-10618. DPC-817 is a cytidine analogue that is active against HIV-1 and HIV-2, and against wild-type virus and viruses with zidovudine- and lamivudine-associated resistance mutations. The compound has a 90% inhibitory concentration (IC_{90}) of approximately 5 µM against wild-type and zidovudine- or lamivudine-resistant virus. It currently is in phase I pharmacokinetic and dose-ranging studies in HIV-1-infected individuals. BCH-10618 is a heterosubstituted cytidine analogue with potent activity against wild-type virus (IC_{90} of 0.02-4.2 µM). It exhibits an additive or synergistic effect in combination with stavudine, didanosine, zidovudine, abacavir, and nevirapine and an additive effect with lamivudine and saquinavir. Repeated passaging of virus in vitro results in emergence of K65R, V75I, and M184V mutations associated with a 1.6- to 4.3-fold decrease in susceptibility. Lamivudine-resistant virus has a 3-fold decreased susceptibility to the compound. Virus with the multi-nRTI resistance codon 69 insertion and Q151M mutations exhibits 6.9-fold and 20-fold decreases in susceptibility, respectively, to the compound.

NNRTIs in development include quinazolinone-based compounds, TMC-120, and SJ-3366. The quinazolinones (DPC-961, -963, -082, and -083) are molecular cousins of efavirenz that exhibit a plasma IC_{90} of 11 to 40 nM and 5- to 50-fold greater activity than efavirenz against wild-type virus and K103N mutants; they also exhibit activity against Y181C mutants. Like efavirenz, the compounds have serum half-lives of approximately 90 hours. They are metabolized by cytochrome P450 3A4 and 2B6 isoenzymes, and thus may pose difficulties with drug interactions.

TMC-120 and TMC-125 are potent agents (IC_{50} and IC_{90} of TMC-120 are 1.5 nM and 3.4 nM, respectively) developed to retain activity against virus resistant to currently available NNRTIs. At 200 nM, TMC-125 selected for the L100I/Y181C resistant variant after 21 days in vitro, with resistance to the compound requiring at least 2 mutations (de Béthune et al, *Antiviral Ther,* 2001). The compound retains activity in vitro against mutants with high-level resistance to other NNRTIs, with some loss of susceptibility being observed with the K103N/L100I mutant (Gruzdev et al, 8th CROI, 2001). In a randomized, placebo-controlled phase I/II trial, TMC-120 at 50 and 100 mg twice daily reduced plasma HIV-1 RNA by 1.44 $\log_{10}$ and 1.51 $\log_{10}$, respectively, at 8 days (Gruzdev et al, 8th CROI, 2001). Doses up to 900 mg twice daily currently are being evaluated in a phase IIA trial (Gruzdev et al, 41st ICAAC, 2001).

SJ-3366 is an agent in preclinical development that is active against HIV-1 and HIV-2, and it appears to act both as a reverse transcriptase inhibitor and as an entry inhibitor interfering with ability of virus to penetrate the cell membrane after attachment. Repeated passage in vitro results in loss of entry inhibition activity, with further passaging resulting in selection of mutations associated with NNRTI resistance (Buckheit et al, *Antiviral Ther,* 2001).

New protease inhibitors in development include atazanavir (BMS-232632), tipranavir boosted with ritonavir, mozenavir (DMP-450), DPC-681 and DPC-684, and TMC-114 and TMC-126. Atazanavir is an azapeptide compound that can be given once daily and that has shown activity comparable to that of other first-generation protease inhibitors as single-agent treatment in phase II/III studies. Although it retains activity against some protease inhibitor-resistant mutants, resistance overlaps with that of other protease inhibitors as more mutations develop. The agent is well tolerated, with dose-dependent hyperbilirubinemia, usually asymptomatic, appearing to be the primary dose-limiting toxicity. In addition to once-daily dosing, a potential advantage of the compound is the relative absence of metabolic toxicity in the form of elevated cholesterol and triglyceride levels reported in association with other protease inhibitors (Figure 1; Squires, 8th CROI, 2001).

There is renewed interest in tipranavir due to the ability to augment activity when combined with ritonavir as a pharmacokinetic enhancer, and to the

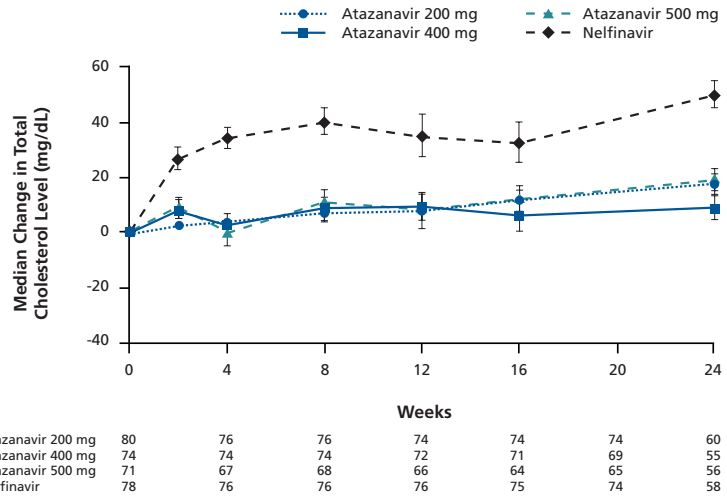

Figure **1.** Median change in total cholesterol level in patients receiving atazanavir 200, 400, or 500 mg or nelfinavir over 24 weeks. Adapted with permission from Squires et al, 8th CROI, 2001.

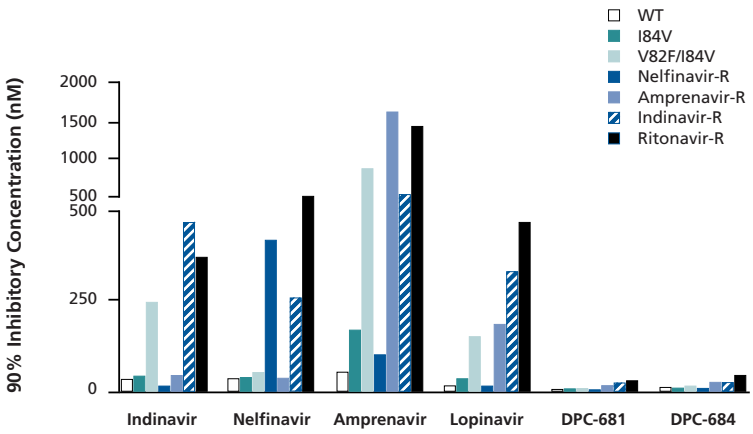

Figure **2.** Ninety percent inhibitory concentrations of DPC-681 and DPC-684 and other protease inhibitors against wild-type (WT) virus and protease inhibitor-resistant (R) virus. Adapted with permission from Erickson-Viitanen et al, 8th CROI, 2001.

demonstrated in vitro activity against virus with multiple protease inhibitor resistance mutations. Tipranavir exhibits in vitro activity against viral variants with a more than 10-fold decreased susceptibility to 3 or more protease inhibitors (Larder et al, AIDS, 2000). In a recently reported open-label phase II study in multiple protease inhibitor-experienced but NNRTI-naive patients, regimens of tipranavir 500 or 1000 mg twice daily and ritonavir 100 to 200 mg twice daily with efavirenz and 1 nRTI resulted in median decreases in plasma HIV-1 RNA levels of 2.59 to 2.69 $\log_{10}$. Decreases to less than 400 copies/mL and to less than 50 copies/mL occurred in 50% to 78% and 50% to 61% of patients, respectively, with median CD4+ increases of 111 to 130 cells/µL at 24 weeks (Curry et al, 1st IAS Conf, 2001). The regimen was relatively well tolerated, with gastrointestinal effects, dizziness, abnormal dreams, and increased liver enzymes being the most commonly reported adverse effects.

Mozenavir is a nonpeptidomimetic, water soluble, cyclic urea compound that has been associated with 2.5- to 3-$\log_{10}$ decreases in plasma HIV-1 RNA levels in phase I/II studies. It is active against virus with the signature D30N nelfinavir resistance-associated mutation and the L90M mutants with decreased susceptibility to a number of other protease inhibitors. In a dose-ranging study assessing mozenavir, in doses of 750 mg 3 times a day, 1250 mg twice daily, or 1250 mg 3 times a day, compared with standard doses of indinavir, both in combination with lamivudine and stavudine, plasma HIV-1 RNA levels were reduced to below 50 copies/mL in 75% to 80% of patients receiving mozenavir-based treatment and in 70% of those receiving indinavir-based treatment. Mozenavir-based regimens were generally well tolerated (Sierra-Madero, 1st IAS Conf, 2001).

DPC-681 and DPC-684 are potent compounds, with an IC_{90} of 4 to 8 nM against wild-type virus and activity against non-clade B and group O virus. These compounds exhibit a median IC_{50} (10-11 nM) approximately 5- to 10-fold lower than currently approved protease inhibitors against virus from patients in whom protease inhibitor regimens that had 3 to 11 protease inhibitor resistance mutations had failed. Plasma drug levels of these compounds, ranging from 0.7 to 1 µM, have been reported to inhibit 90% of isolates resistant to first generation protease inhibitors (Bacheler et al, *Antiviral Ther,* 2001). Figure 2 shows the comparative potency of the compounds against resistant strains (Erickson-Viitanen et al, 8th CROI, 2001).

TMC-114 and TMC-126 are among the new class of "resistance-repellent" agents that are designed to have high affinity at active sites but to be physically flexible. TMC-126 exhibits an IC_{50} of approximately 10^{-10} M against wild-type isolates. Both compounds are active against a wide panel of multiple protease inhibitor-resistant isolates. TMC-114 is currently in phase I dose-ranging studies in healthy volunteers, with no maximum tolerated dose having yet been reached (Erickson, 8th CROI, 2001; van der Geest, 41st ICAAC, 2001).

The entry inhibitor pentafuside is a potent gp41 fusion inhibitor (also active against non-clade B virus) that exhibits IC_{50} values for viruses resistant to nRTIs, NNRTIs, and protease inhibitors similar to IC_{50} values for wild-type virus. The agent was shown to produce sustained decreases in plasma HIV-1 RNA at 16 weeks in patients with virus resistant to agents from all 3 drug classes. However, resistance to the agent emerged during clinical studies in treatment-experienced patients. T-1249 is a 39-amino acid linear synthetic peptide active at the HR2 region of gp41, overlapping the active site of pentafuside. The compound has an IC_{90} of less than 100 ng/mL and exhibits activity independent of previous exposure to or presence of multiple resistance mutations to nRTIs, NNRTIs, or protease inhibitors (Miralles et al, *Antiviral Ther,* 2001). Resistance to T-1249 is difficult to select for in vitro, and pentafuside-resistant isolates generally are susceptible to T-1249. In early testing in treatment-experienced patients with multidrug-resistant virus, plasma HIV-1 RNA decreases of 0.4, 0.8, and 1.3 $\log_{10}$ have been achieved with once-daily doses of 12.5, 25, and 50 mg (Eron et al, 8th CROI, 2001).

CCR5-receptor inhibitors are under development by a number of pharmaceutical companies. The Schering C compound, currently the most widely known example, is a CCR5 antagonist of small molecular weight that exhibits little binding to other G-coupled proteins, and has an IC_{90} of approximately 20 nM for CCR5-utilizing virus; it has no activity against CXCR4-utilizing virus. Resistance to the compound can be selected for in vitro, but resistant virus still uses CCR5 for cell binding. The compound does not induce cytochrome P450 3A4, 2D6, 2C9, or 2C19 enzymes. Single-dose studies in humans indicate that 25 to 600 mg results in blood levels above 20 nM for more than 20 hours, with doses of 400 to 600 mg achieving levels above the IC_{90} for 96 hours. Asymptomatic cardiac conduction abnormalities were observed at high doses in early studies, the clinical significance of which is unknown.

Integrase inhibitors, which interfere with the strand transfer step in viral inte-

gration, are in development, although no lead compound has yet been identified. Compounds studied thus far (L-731-988, -708-906, -731-927, and -731-942) have exhibited good in vitro activity. Loss of activity has been reported to require acquisition of integrase active site mutations T66I, S153Y, and M154I; mutants have reduced replicative fitness, with virus with all 3 mutations being nonviable (Hazuda et al, *Antiviral Ther*, 2001).

In summary, a number of compounds in development have promise as agents active against virus isolates resistant to currently available antiretroviral drugs, or as agents active against new viral targets. Their clinical activity and where they fit in our current approaches to antiretroviral therapy must await further investigation.

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Suggested Reading

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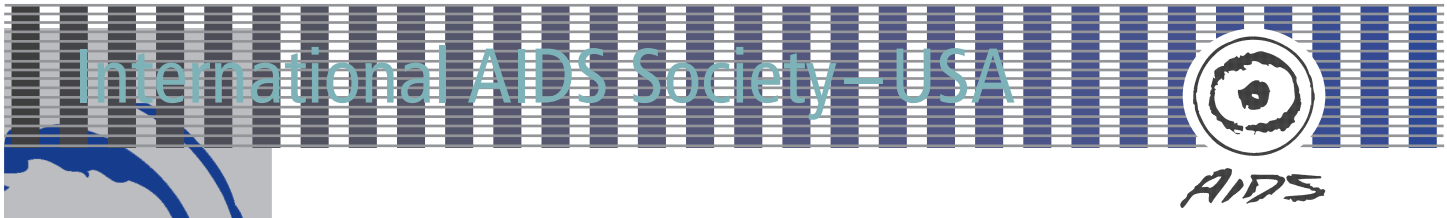

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Perspectives

Science and Treatment of HIV and Hepatitis C Virus Coinfection

Characteristics and management of hepatitis C virus infection in patients with HIV infection were discussed at the San Francisco International AIDS Society–USA course in April, 2001, by Stuart C. Ray, MD.

An estimated 170 million people worldwide are infected with hepatitis C virus (HCV), including approximately 3 million in the United States. Hepatitis C virus disease accounts for approximately 10,000 deaths annually in this country, with this number expected to increase by 2- or 3-fold by 2020. It is estimated that HCV coinfection is present in 30% (approximately 240,000) of the individuals with HIV infection in the United States.

There are 6 known clades of HCV; genotype 1 accounts for most infections worldwide and in the United States and is the genotype least responsive to interferon alfa treatment, the standard therapy for HCV infection. Hepatitis C virus infection is characterized by a high rate of viral replication (10^{11}-10^{12} virions/day). Chronic infection is established in the majority of, but not all, cases of infection. Hepatitis C virus infection is eradicable, since there is no latent form of infection.

Transmission

The risk of HCV infection compared with HIV infection is approximately 10 times higher following parenteral exposure (eg, 5% vs 0.5%, respectively, following needlesticks from infected source) and 5 times lower following perinatal exposure (eg, 5% vs 25% risk of vertical transmission from untreated mothers). The majority of injection drug users may be infected with HCV; in one study conducted in Baltimore, HCV infection was present in approximately 80% of injection drug users within 10 months of starting drug use (compared with hepatitis B virus infection, which was present in approximately 60%, and HIV infection, present in approximately 20%; Garfein et al, *Am J Public Health*, 1996). Available data suggest that risk of perinatal HCV transmission is greatly increased in cases of HIV/HCV coinfection, with risk of HIV transmission also being increased somewhat by the presence of HCV infection (Figure 1; Zanetti et al, *Lancet*, 1995; Hershow et al, *J Infect Dis*, 1997).

Sexual transmission of HCV is supported by findings indicating sexual exposure as the only apparent exposure in some cases and epidemiologic data suggesting that high-risk sex is associated with a high HCV infection prevalence. However, other data show a low prevalence of infection in the monogamous sex partners of HCV-infected individuals. For example, spouses of HCV-infected men with hemophilia have a prevalence of HCV infection identical to that in the general population despite exposure over prolonged periods via unprotected sex. In addition, non-injection drug using men who have sex with men have a prevalence of HCV infection similar to that in the general population. Part of the problem in defining risk through sexual exposure may be poor ability to determine the effects of remote percutaneous exposures (eg, exposure through injection drug use in the 1970s).

Natural History of HCV Infection

Approximately 90% of individuals have no symptoms during the acute phase of HCV infection, making acute infection difficult to identify (CDC, MMWR, 1998). Infection resolves in approximately 15% of patients within 2 years and becomes chronic in the remainder. Of those with chronic infection, infection remains stable (absence of significant liver disease) in approximately 80%, whereas 20%

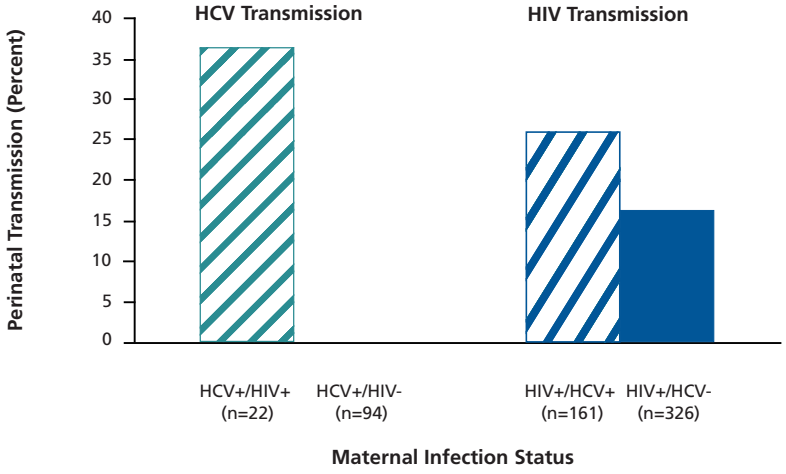

Figure **1.** Effects of HIV/hepatitis C virus (HCV) coinfection on perinatal transmission of HIV and HCV. Rates of HCV transmission (green bar, left) are shown according to whether HCV-infected mother had HIV infection (HIV+) or not (HIV-). Adapted from Zanetti et al, *Lancet,* 1995. Rates of HIV transmission (blue bars, right) are shown according to whether HIV-infected mother had HCV infection (HCV+) or not (HCV-). Adapted with permission from Hershow et al, *J Infect Dis,* 1997.

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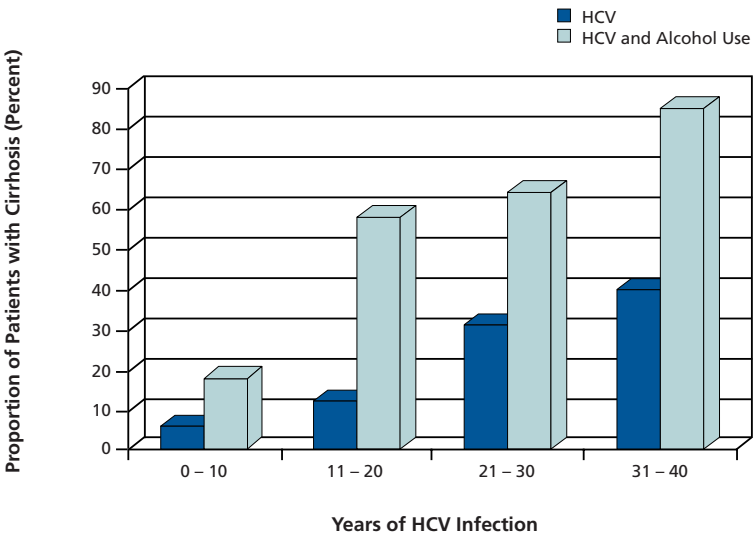

Figure **2.** Association of alcohol use with development of cirrhosis in hepatitis C virus (HCV)-infected patients. Alcohol use was defined as more than 40 g alcohol/day in women and more than 60 g alcohol/day in men for more than 5 years. Adapted with permission from Wiley et al, *Hepatology,* 1998.

(17% overall) progress to cirrhosis. Of those with cirrhosis, the disease is slowly progressive in 75%, with 25% (4% overall) progressing to end-stage liver disease (hepatocellular carcinoma, transplantation, or death).

Data from a number of studies show that consumption of alcohol greatly increases risk of development of cirrhosis in HCV-infected individuals (Figure 2; Wiley et al, *Hepatology*, 1998). The increases in relative risk in the various studies range from 2- to 10-fold and increased risk is evident irrespective of magnitude of alcohol use. Extrahepatic manifestations of HCV include cryoglobulin disease, porphyria cutanea tarda, and lichen planus; type 2 diabetes and lymphomas have also been linked with HCV infection (Mehta et al, *Ann Intern Med*, 2000; Kitay-Cohen et al, *Blood*, 2000).

Effect of HIV Infection on HCV Infection

Hepatitis C virus infection has been designated as an opportunistic infection in HIV infection, in recognition of its increased prevalence and greater severity in patients with HIV infection. One recent study showed that significantly more coinfected patients had HCV viral loads in the highest viral load quartile compared with patients with HCV infection alone (Thomas et al, *J Infect Dis*, 2000). It should be noted, however, that magnitude of HCV viral load has not been associated with increased risk for end-stage liver disease. Other data show that time to cirrhosis progression is markedly reduced in HIV-infected patients with lower CD4+ cell counts and in those with greater alcohol consumption compared with HIV-uninfected patients (Figure 3; Benhamou et al, *Hepatology*, 1999).

A particularly important study of the prognostic effect of HIV coinfection on HCV-related mortality from hepatic failure was performed in a United Kingdom hemophilia population followed from 1969 to 1993. This study showed that risk of liver disease-related death was increased by approximately 17-fold in HCV-infected individuals and by approximately 90-fold in HIV/HCV-coinfected individuals compared with the general population (Darby et al, *Lancet*, 1997).

Effect of HCV Infection on HIV Infection

One way in which HCV infection may complicate HIV infection is via its effect on antiretroviral therapy. A study in 298 patients beginning antiretroviral therapy with protease inhibitors and nucleoside reverse transcriptase inhibitors in the Johns Hopkins HIV Cohort showed that HCV infection was associated with a 3.7-fold increased risk of severe (grade 3 or 4) elevation in transaminase levels among subjects receiving antiretrovirals other than ritonavir (Sulkowski et al, JAMA, 2000). However, 88% of HCV-infected patients did not develop severe hepatotoxicity. Assessment of hepatotoxicity by antiretroviral drug used indicated that severe toxicity was more common with ritonavir (Figure 4). Although risk was somewhat greater among

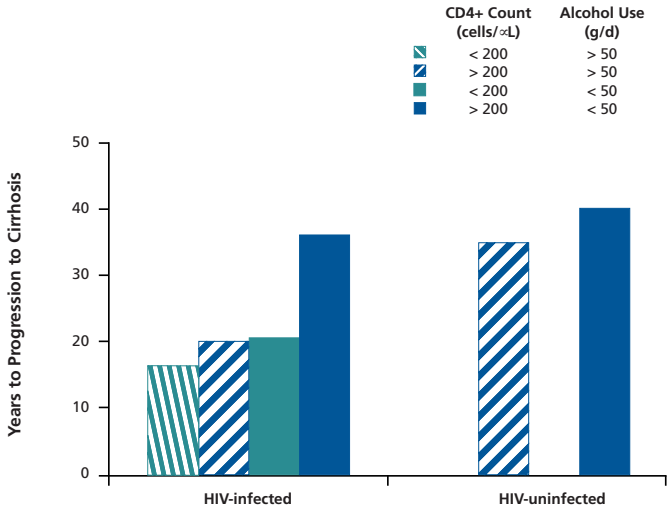

Figure **3.** Years to progression to cirrhosis in hepatitis C virus-infected patients with or without HIV infection according to CD4+ cell count greater or less than 200/µL and alcohol use greater or less than 50 g/day. Adapted with permission from Benhamou et al, *Hepatology,* 1999.

patients receiving ritonavir for pharmacokinetic enhancement of saquinavir, it was not significantly different from that observed with use of ritonavir alone.

Other data have indicated that HCV coinfection worsens the outcome of HIV infection. In the Swiss HIV Cohort Study among more than 3000 patients beginning potent antiretroviral therapy between 1996 and 1999, HCV infection (present in 37% of the population studied) was associated with a relative risk of progression to AIDS or death of 1.7. Hepatitis C virus seropositivity was also associated with a 3.5-fold relative risk for HIV viral load persistently greater than 400 copies/mL, compared with patients without HCV infection, as well as with suppressed CD4+ cell count rebound after initiation of antiretroviral therapy (Greub et al, *Lancet*, 2000). In total, 88% of those with HCV infection had a history of injection drug use; the greatest rate of progression of HIV disease was among HCV-infected patients who were active injection drug users. A drawback of these data is that they do not account for duration of exposure to antiretroviral therapy. Data from the Johns Hopkins HIV Cohort do not show a difference in HIV disease progression rates between HCV-infected and HCV-uninfected patients after correction for time on antiretroviral therapy (M. S. Sulkowski, MD, personal communication).

Management of HCV Infection

Dr Ray noted that the standard therapy for HCV infection has been interferon alfa. Interferon alfa is an immune-stimulating and antiviral agent that acts via host cellular proteins. Thus, it does not appear to select for resistance via mutations in target viral components. Unlike HIV infection and antiretrovirals, prior treatment of HCV infection with interferon alfa does not reduce the likelihood of response to a subsequent course. The most common regimen is 3 MU 3 times weekly. Although this regimen produces initial decreases in HCV viral load that are significantly smaller than those produced by daily regimens of 3 MU or higher, it is better tolerated and is no less likely than more intense regimens to produce sustained virologic response. Nevertheless, recent pharmacodynamic analyses suggest that 3-times-a-week dosing of conventional interferon alfa may be suboptimal, and that the high, sustained drug levels associated with pegylated interferon products may explain their greater efficacy (Zeuzem et al, N Engl J Med, 2000; Heathcoate et al, N Engl J Med, 2000; Lindsay et al, Hepatology, 2001; Manns et al, Lancet, 2001; Zeuzem et al, Gastroenterology, 2001).

Sustained response to interferon alfa treatment generally is defined as HCV viral load below the limits of detection using a sensitive HCV RNA assay at 6 months after completion of therapy. Patients with such response have a likelihood of less than 2% per year of becoming viremic again. Relapse is defined as an elevation of HCV viral load

> Studies suggest that the high, sustained drug levels associated with pegylated interferon alfa may explain its greater efficacy compared with conventional interferon alfa

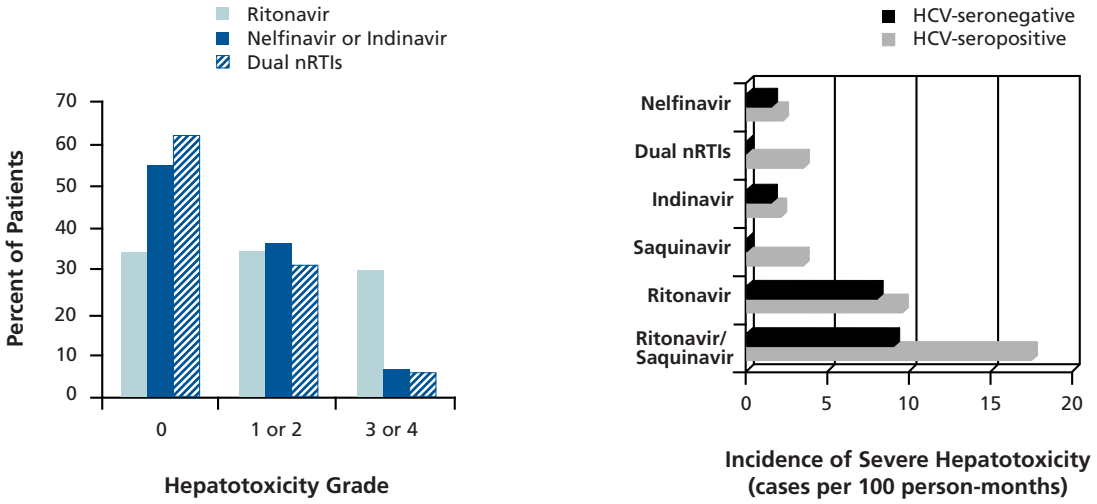

Figure **4.** Antiretroviral-associated hepatotoxicity (elevation of alanine aminotransferase or aspartate aminotransferase) by drug used (left) and incidence of severe hepatoxicity according to drug used and presence or absence of hepatitis C virus (HCV) infection (right) in patients in the Johns Hopkins HIV Cohort initiating antiretroviral therapy between January 1996 and January 1998. nRTI indicates nucleoside reverse transcriptase inhibitor. Adapted from Sulkowski et al, *JAMA,* 2000.

following initial suppression. If it occurs, it usually does so within several weeks following completion of interferon alfa therapy, with viral load initially rebounding beyond and then returning to the pretreatment level.

The combination of interferon alfa and ribavirin is more effective than interferon alfa alone in HIV-uninfected patients. Ribavirin appears primarily to decrease the proportion of patients having viral relapse rather than decreasing the proportion of patients with no response (absence of decrease in viral load) to treatment. Studies of the efficacy and safety of combined treatment in HIV/HCV-coinfected patients are under way.

Factors affecting rates of sustained virologic response to interferon alfa plus ribavirin therapy are shown in Figure 5 (Poynard et al, *Lancet*, 1998). Fairly high sustained virologic response rates are achieved in patients infected with HCV genotype 2 or 3, irrespective of initial viral load. Sustained virologic response rates are lower in patients infected with genotype 1, 4, or 5. In such patients with high initial viral load, 48 weeks of therapy produces markedly greater response rates than 24 weeks of therapy. Currently, treatment is given for 6 months in patients infected with genotype 2 or 3 and for 1 year in patients infected with genotype 1, 4, or 5. Pegylated interferon alfa formulations have improved pharmacokinetics, and, as discussed above, data are accumulating to show therapeutic superiority of these products over standard interferon alfa.

Adverse effects of interferon alfa treatment include fever and aches (approximately 70% of patients), depression (including rare suicide attempts among patients without prior psychiatric history [Fukunishi et al, *Burns*, 1998; Rifflet et al, *Gastroenterol Clin Biol*, 1998; Zdilar et al, *Hepatology*, 2000]), neutropenia and thrombocytopenia (generally within the first month of treatment), thyroid dysfunction, and hair thinning (typically reversible). Recombinant human granulocyte colony-stimulating factor (rhu G-CSF; filgrastim), although not indicated for such use, has been successful in ameliorating neutropenia and is undergoing formal study in this setting. Thrombocytopenia generally is mild and does not require cessation of treatment. Thyroid dysfunction, consisting of initial hyperthyroidism followed by hypothyroidism, is observed in nearly 5% of patients, and is permanent in some. Adverse effects of ribavirin include anemia, teratogenicity, and gout. Recombinant human erythropoietin (epoetin alfa) has been successfully used to improve hematocrit in some anemic patients and formal evaluation of this investigational use is under way.

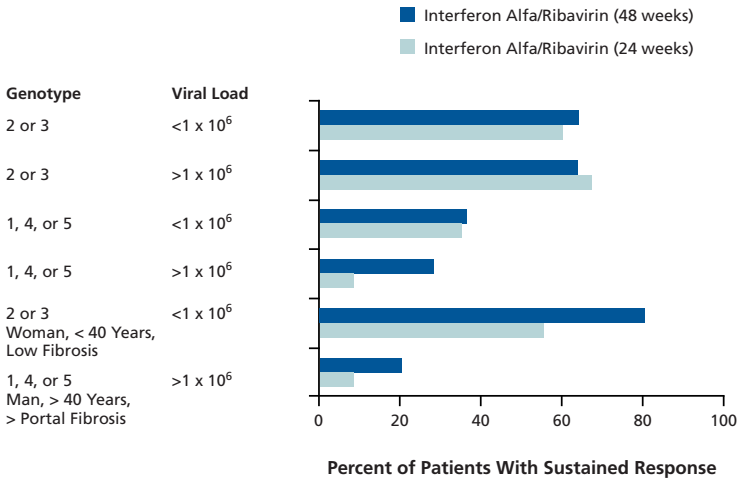

Figure **5.** Factors affecting sustained virologic response rates in hepatitis C virus (HCV)-infected patients receiving interferon alfa 3 times weekly plus ribavirin. Figure shows percentage of patients with sustained response according to infecting HCV genotype, initial viral load, and duration of therapy. The 2 bottom rows show response rates in a "best case" scenario (ie, a woman younger than 40 years with low fibrosis and genotype and viral load as shown) and a "worst case" scenario (ie, a man older than 40 years with worse than portal fibrosis and genotype and viral load as shown). Adapted with permission from Poynard et al, *Lancet,* 1998.

Adverse effects of interferon alfa include fever, aches, depression, neutropenia and thrombocytopenia, thyroid dysfunction, and hair thinning

Goals of treatment for HCV infection depend on the HIV and HCV infection status of the patient. Cure of HCV infection (viral eradication) is the goal in patients with preserved immune function and less advanced HCV infection. Goals are histologic and clinical in patients with poor response to interferon alfa therapy or advanced HIV disease, with the aims of treatment being to delay hepatic fibrosis and cirrhosis and prevent hepatic decompensation and hepatocellular carcinoma. There is evidence that clinical benefit is derived even when interferon alfa therapy does not produce sustained response. As shown in one study, progression of fibrosis on liver biopsy was reduced in patients with unsustained response to interferon alfa therapy compared with that in patients receiving no treatment (Figure 6; Shiratori et al, *Ann Intern Med*, 2000).

Screening for HCV infection in HIV-infected patients should be performed using enzyme immunoassay HCV antibody testing. Such screening has failed to detect cases of infection (as determined by HCV RNA testing) in patients with antibody-negative HCV infection (Bonacini et al, *J Acquir Immune Defic Syndr*, 2001). However, the frequency of such occurrences appears to be minimal, and in some cases may be due to cross-sec-

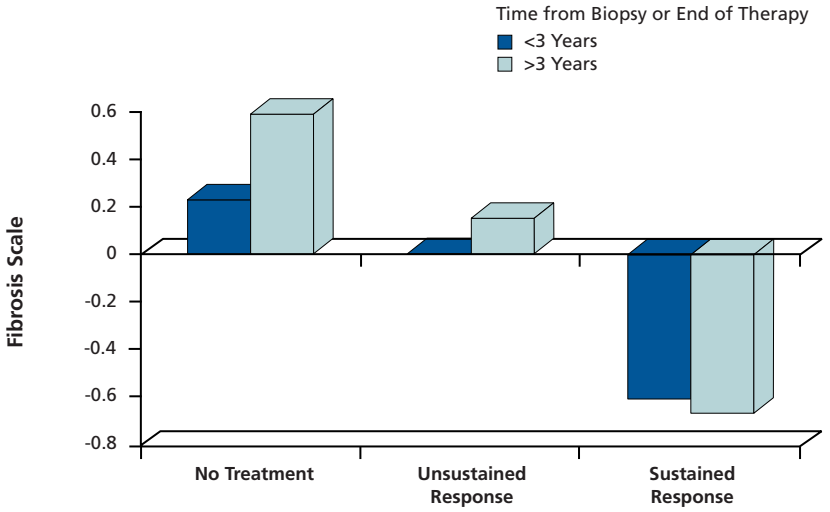

Figure **6.** Change in fibrosis stage on the METAVIR fibrosis scale in patients with hepatitis C virus infection according to whether they received no treatment or had unsustained or sustained response to interferon alfa therapy and according to the interval between biopsies (greater or less than 3 years). Adapted from Shiratori et al, *Ann Intern Med,* 2000.

tional study design, resulting in detection of acute infections. A longitudinal study of 559 patients with detectable serum HCV RNA in the Johns Hopkins HIV Cohort showed that all but 1 were HCV antibody-positive when a third-generation enzyme immunoassay was used, with this patient seroconverting at 6-month follow up (Thio et al, J *Clin Microbiol*, 2000). Screening should also include HCV RNA testing in any patient with acute hepatitis or unexplained alanine aminotransferase elevation.

Evaluation of patients found to be HCV antibody-positive includes evaluation for other important causes of liver disease, in addition to testing that will guide management. Screening for other causes of liver disease should be guided by individualized personal and family history, but might include screening for iron overload, Wilson disease, alpha$_1$ antitrypsin deficiency, and autoimmune hepatitis. To guide prophylaxis and treatment decisions, one should consider testing for hepatitis A virus and hepatitis B virus infection and immunization, depression, HCV RNA levels (qualitative test results for diagnosis and quantitative results for baseline and follow-up viral load), and infecting HCV genotype. A patient's ability to adhere to interferon alfa therapy should also be evaluated. In patients without a major contraindication (markedly elevated prothrombin time or severe thrombocytopenia), biopsy provides important prognostic information by assessing degree of fibrosis, and thus assists in guiding treatment decisions. Although biopsy is not a prerequisite for treatment, neither HCV RNA levels nor alanine aminotransferase elevations are good predictors of prognosis.

Because untreated HIV infection is uniformly fatal, treatment of HIV disease remains the primary focus of therapy in coinfected patients. However, it is not clear whether treatment for HIV infection should precede treatment for HCV infection, or vice versa. HCV infection treatment decisions should be based on biopsy findings, with biopsy being performed every 2 or 3 years. In patients with advanced liver fibrosis (stage 3 or 4), treatment should be initiated regardless of CD4+ cell count to prevent death from hepatic failure. For mild to moderate fibrosis, treatment should be initiated in patients with stable HIV disease and preserved immune function (CD4+ cell count >350/µL), with the objective being cure of the HCV infection. Observation should be considered in patients with no or minimal fibrosis. Treatment is not recommended in patients who already have decompensated liver disease.

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Original Contribution

Curtailing the HIV Epidemic: The Power of Prevention

Michael H. Merson, MD

Michael H. Merson, MD, delivered a keynote address on global HIV prevention programs at Curtailing the HIV Epidemic: The Power of Prevention Leadership Forum*, a meeting of international leaders, policymakers, and program planners held in New York City on June 22, 2001, immediately prior to the United Nations General Assembly Special Session on HIV/AIDS. The Henry J. Kaiser Family Foundation, the Ford Foundation, and the Bill and Melinda Gates Foundation were hosts of the forum. The meeting, like Dr Merson's speech, focused on the role of prevention in the global fight against HIV, and examined effective prevention strategies, the barriers to their implementation, and the relationship between prevention and care. The edited text of Dr Merson's speech is printed below.*

I have been asked to present evidence to support the efforts for HIV prevention. I will do this by reviewing the context in which prevention must succeed, the essential elements of a successful HIV prevention strategy, and the actions required for prevention to work effectively. A most unfortunate and needless debate has emerged about the merits of HIV prevention as opposed to care. Both are crucial efforts and each must be greatly scaled up. Prevention and care are complimentary and synergistic, and efforts to prioritize one at the expense of the other are unethical, a denial of a fundamental human right, and just plain bad public health.

The Context

This is now the twentieth year of the most devastating pandemic in the history of modern civilization. The bubonic plague of the Middle Ages killed as many people, but its spread across the globe was not nearly as rapid and its acute impact thus not nearly as profound.

Since 1990, the total number of HIV infections has increased 10-fold—from 6 million to nearly 60 million—and it is nowhere near its peak. Those living in sub-Saharan Africa have suffered the most. Across the African continent, there are now 25 million persons living with HIV and AIDS, the health care system has become an AIDS care system, and more than 10 million children have been orphaned. In the countries of Southern Africa, 20% of the adult population is infected, and in less than a decade, life expectancy has dropped by 15 to 20 years.

During the past decade the pandemic has gradually extended throughout Asia, from Thailand and the countries in the Golden Triangle, to China, where the extent of its spread is not fully known, to India, which has, or soon will have, more infections than any other country. In China injection drug use and contaminated blood have fueled HIV spread, whereas in India heterosexual transmission has been the prominent mode of transmission.

In the Ukraine, Russia, and the rest of Eastern Europe, where the social conditions could not be more ideal for the spread of the virus, the pandemic started slowly, but is now expanding at an exponential rate. Injection drug use has been the primary cause of infection, but rates of heterosexual transmission are rapidly rising.

In the Western Hemisphere, the Caribbean countries presently have the second highest rates of HIV infection globally, while in Central and South America the pandemic continues to surface in diverse and vulnerable populations. In the United States, the epidemic has "stabilized," but at an appalling rate of

> India has, or soon will have, more HIV infections than any other country

40,000 new infections per year. The majority of these infections occur in populations of color, and rates of infection are increasing in men who have sex with men (as they are in Western Europe), due to complacency about prevention, enhanced by the availability and effectiveness of antiretroviral therapy.

In some countries, prevention programs have achieved considerable success, but for the most part, the response to the pandemic has been delayed, inappropriate, or insufficient. As an infection transmitted primarily by sex or by illicit drug use and associated with stigmatized and marginalized groups, HIV has all too often engendered moralistic or repressive responses rather than sound public health actions. In addition, the response of the international community has been grossly insufficient. As just one example, development assistance for anti-AIDS efforts in the least developed and other low-income countries reached a maximum of a paltry $144 million a year during most of the 1990s, and was a mere $70 million a year in Africa between 1996 and 1998.

The good news is that the context is changing, and as UNAIDS Executive Director Peter Piot said at the recent World Health Assembly, we are witnessing a "sea change" in the international response to the pandemic. This can be seen, for exam-

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ple, in the World Bank's heightened commitment, particularly for Africa, where by next year it projects the approval of 1 billion new dollars in credits to scale up prevention and care efforts in 25 countries. The major international foundations, such as those hosting this Power of Prevention Leadership Forum—the Henry J. Kaiser Family Foundation, the Ford Foundation, and the Bill and Melinda Gates Foundation—have also dramatically increased their support to HIV/AIDS activities.

> Prevention programs can reverse a major epidemic, as in Uganda and Zambia, and contain an emerging epidemic, as in Thailand and Brazil

Some of this "sea change" is due to increased awareness about the pandemic's severity, much of it a result of the convening of the XIII International AIDS Conference in Durban in July, 2000. Some of it is related to the new and exciting developments in the search for an HIV vaccine and the serious efforts underway—after years of little more than neglect—to find a safe and effective microbicide.

But probably the greatest impetus for this turning point in the international response has been global concern about equity in access to antiretroviral drugs in low- and middle-income countries. This concern originated with the use of these drugs, given to pregnant women near or at delivery, to successfully interrupt mother-to-child transmission. Greater equity in access to antiretroviral drugs was made a reality by the substantial reduction in price in these countries during the past 6 months, and by the remarkable success reported by Brazil in reducing AIDS-related mortality, hospitalizations, and opportunistic infections, as well as the overall costs of AIDS care, achieved in part through the widespread use of these drugs.

For the first time in the pandemic's history, comprehensive AIDS care is now a reality for everyone.

Elements of Prevention

If this is the context in which HIV prevention now operates, what should be the main elements of an effective prevention strategy?

The success of behavioral HIV prevention interventions—whether directed toward individuals, couples, families, communities, or society at large—in reducing sexual transmission and transmission through injection drug use has been well documented. In fact, social and behavioral scientists have been able to provide more scientific evidence of their effectiveness than exists for prevention of most other behavior-related diseases.

In addition, a growing number of countries have documented the success of their prevention efforts through careful program evaluations and well-designed surveys. There should be no doubt in our minds that prevention programs can reverse a major epidemic, as has been seen in Uganda and Zambia; can contain an emerging epidemic, as has occurred in Thailand and Brazil; and can avoid an epidemic all together, as has been well documented in Senegal.

There are elements of successful prevention programs worth emphasizing (see summary in Table 1):

- They are tailored to the social and economic conditions and to the social and cultural norms of the populations that need to be reached. Effective HIV prevention messages are based on knowledge and understanding of local attitudes, behaviors, and practices.
- They present information that empowers those who are vulnerable to understand their risk and to know how to protect themselves from infection. This means talking frankly about comprehensive sexual education and harm reduction, especially with youth. In populations where sex during adolescence is the norm, abstinence-only messages place youth at great risk of infection and are equivalent to teenage genocide.
- They involve those who are infected by the virus, as well as members of civil society, ranging from women's groups to gay men's AIDS service organizations to families caring for orphans.
- They take place within a supportive legal and policy framework, which protects HIV-infected persons and those vulnerable to infection from discrimination in all its ugly forms, and assures them the right to liberty and security before the law, as well as the right to marry, find a family, and have equal access to education and employment. This entails the elimination of forced HIV testing and the repealing of laws that criminalize homosexuality and commercial sex work.
- They are multifaceted and multisectoral; there is no single magic bullet.
- They are sustained over time, as populations at risk change. Prevention must be reinvented over and over to keep reaching the next audience and to be heard and believed.
- And last, and some would say most importantly, they require

Table **1.** Elements of Successful HIV Prevention Programs

1. Programs are tailored to the social and economic conditions and social and cultural norms of the target populations
2. Information is presented that empowers those who are vulnerable to understand their risk and know how to protect themselves
3. Programs involve HIV-infected persons and members of civil society
4. A supportive legal and policy framework protects HIV-infected and at-risk persons from discrimination and infringements of their human rights
5. Programs are multifaceted and multisectoral
6. Programs are sustained and reinvented as populations at risk change
7. Strong and committed political leadership mobilizes the entire country toward HIV prevention goals

strong political leadership that is committed to HIV prevention goals and mobilizes all government ministries, civil society, and the private sector toward this common goal.

There are two other important points to make about HIV prevention. First, HIV prevention strategies—including condom promotion, voluntary counseling and testing, treatment of sexually transmitted diseases, and harm reduction interventions in injection drug users—are highly cost-effective and have the greatest benefit when HIV prevalence is low and they are targeted to high-risk groups. Political leaders should not doubt their effectiveness, nor be concerned about their cost.

Second, in a number of ways, the increasing availability of antiretroviral drugs should benefit prevention efforts. Persons who believe they may be infected, no longer fearing a death sentence, are more likely to seek voluntary counseling and testing. If they are found to be HIV-seronegative, this offers a prime opportunity to deliver prevention messages. If they are found to be infected, the treatment setting provides an ideal time to repeatedly reinforce these messages. This is particularly important, since it has been shown that those receiving antiretroviral therapy can have demonstrable increases in high-risk behavior and sexually transmitted diseases.

The availability of antiretroviral therapy for pregnant mothers encourages them to come for testing as a means of preventing infection in their newborn. Continuing this treatment in mothers after delivery will allow them to breast-feed more safely, which is important for preventing diarrhea and malnutrition in their infants.

Also, at a societal level, the removal of the death sentence from AIDS will no doubt reduce the stigma around HIV infection. In turn, this should decrease discrimination against HIV-infected persons.

Finally, it is possible that antiretroviral therapy—if provided to most of those in need—may have the added prevention benefit of lessening the likelihood of sexual transmission by decreasing the viral load in genital secretions.

Comprehensive care has other types of prevention benefits. It keeps families together longer by prolonging the lives of HIV-infected parents, so that children do not have to leave school, and parents do not have to stop working in the field or factory and can save money for the orphan years of their children. Also, by keeping young adults alive longer, it can lessen the impact of the epidemic on a nation's economic development and help to maintain national security.

For all these reasons, there should be no doubt that prevention and care are natural allies and each is equally paramount in the global and national efforts to control the pandemic. Efforts to pit one against another are morally indefensible and scientifically incorrect.

The safe and effective administration of antiretroviral drugs will require training of health care providers, strengthening of counseling and laboratory services, improvement of logistics systems, and small- and large-scale operational research trials to determine the best treatment regimens and operational strategies for monitoring patients. These efforts should always include prevention components, so they can simultaneously strengthen the primary prevention infrastructure and identify novel and innovative ways to deliver prevention strategies.

One of the best ways to stimulate development of the care and prevention infrastructure is to have drugs and condoms to deliver. Everywhere a beginning can be made.

Required Actions

In conclusion, HIV prevention can be elevated to the scale required to curtail the spread of the pandemic through the following measures.

- First and foremost, what has been learned over the past 2 decades about prevention must be applied at dramatically increased levels. We may not know everything we would like to know about HIV prevention, but we know much more than we are doing. Truth must overcome denial. Urgency must replace complacency. Prejudices must be overcome, and erroneous and unfounded assumptions abandoned, such as the belief that those living in low-income countries are unable to take antiretroviral drugs because of dosing schedules, treatment adherence, or drug-resistant superviruses. Cynicism about the effectiveness of HIV prevention must stop. By careful monitoring and vigorous evaluation of programs, their impact can be documented and their deficiencies identified so they can improve as they move forward.
- Research efforts to develop new prevention tools—particularly an HIV vaccine and microbicides—need to be greatly expanded. More incentives and innovative mechanisms are needed to ensure that products that are developed are effective, affordable, and accessible for those who need them the most. Their availability will not remove the need for behavioral interventions. On the contrary, most experts believe that at least for the foreseeable future, available vaccines will provide only modest protection and reduction of transmission of the virus.
- Greater attention must be given to the importance of reducing the social and economic vulnerability of those susceptible to HIV infection. Creating a true power balance between women and men, and providing all women the freedom to exercise control over their own sexuality, as well as education and access to the cash economy, are good places to start. Laws and customs that protect the rights of those infected with HIV should also be vigorously promoted and barriers to them, which allow discrimination to thrive, should be removed. We also need to better understand how to integrate HIV prevention into anti-poverty programs and strategies.

> At least $4 to 5 billion is required annually for global prevention efforts— less than 1% of the world's yearly military spending

- For prevention to succeed as it must, resources of an unparalleled scale are going to be needed. UNAIDS estimates that at least $4 to 5 billion is required annually for global pre-

vention efforts. This is less than 1% of the world's yearly military spending. Some of this money can be obtained through debt relief. Today, African countries pay $15 billion yearly in debt to international creditors, while owing them a staggering $230 billion. This means that they are transferring 4 times more to their creditors than they are spending on national health and education programs. Progress has slowly been made in this area—some $20 million were added to AIDS programs in African countries last year—but this is far short of what is required. A massive escalation of resources is needed.

During the past few months, through the efforts of United Nations Secretary General Kofi Annan and others, a consensus has developed around the establishment of an international global fund to attract the resources needed for HIV prevention and care. Such a fund can make a difference if it attracts new resources; strikes a balance between prevention and care; keeps policy- and decision-making at the national level; supports existing national programs and priorities, including the purchase of antiretroviral drugs; fully involves civil society and the private sector; has a streamlined and transparent secretariat that utilizes highly qualified technical advice and ensures accountability; and respects the principles of ethics and equity. It should not seek to address all the world's health problems, but rather focus on the devastating pandemic and its consequences, such as an exponential increase in tuberculosis.

Are 25 million deaths, the near devastation of the social fabric of many nations, and the real threat that this may happen elsewhere enough to rally world leaders to truly confront this pandemic?

It will take unprecedented cooperation among governments, foundations, civil society, and industry to agree on priorities, strategies, and specific goals and targets, for which all are accountable. It will require governments to forego national and sexual politics and blame, and to acknowledge that vulnerable populations exist everywhere and are equally deserving of their human rights to prevention, care, and social support. When it comes to prevention, the gap between science and policy must close. And it will require high-level leadership in all nations, not yet seen in the history of this pandemic. Leadership means commitment to a moral and humane approach to prevention, ownership of plans and programs, and above all else, courage—courage to talk frankly about human behavior without prejudice; courage to take on controversial issues no matter the political risk; and courage to generate a vision of new responses and understandings that, once and for all, bring an end to this pandemic.

Author Financial Disclosure: Dr. Merson has no affiliations with commercial organizations that may have interests related to the content of this article.

For perspectives on HIV global treatment strategies, see the June, 2001, issue of *Topics in HIV Medicine,* available online at www.iasusa.org/pub/June_Journal.pdf.

Update on Drug Resistance Mutations in HIV-1

Data continue to accumulate about the role of resistance testing in clinical practice. The Drug Resistance Mutations Group of the International AIDS Society–USA (see sidebar) is charged with monitoring the field and maintaining a current list of mutations that impact drug susceptibilities. The Drug Resistance Mutations Group reviewed data presented in June, 2001, at the 5th International Workshop on HIV Drug Resistance and Treatment Strategies in Scottsdale, Arizona, and discussed other recent developments. The figures presented on the following pages have been updated accordingly, since the June, 2001 publication in this journal.

Major revisions made since the June, 2001 publication include:

- New placement of the multidrug-resistance bars at the top of the drug classes.
- New graphic display of the nucleoside reverse transcriptase inhibitor (nRTI)-associated mutations (NAMs; M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E), the mutations associated with cross-resistance to the nRTIs, except lamivudine. The NAMs are shown in light pink vertical lines in the nRTI and nucleotide reverse transcriptase inhibitor classes.
- The addition of 5 mutations that affect the efficacy of lopinavir/ritonavir (V32I, L33F, I50V, I47V, and G73S) based on data presented at the 5th International Workshop on HIV Drug Resistance and Treatment Strategies. Until more data become available, the lopinavir/ritonavir-associated mutations are presented as neither "primary" nor "secondary."

These figures will be updated regularly and will be available on the International AIDS Society–USA Web site, www. iasusa.org.

The Drug Resistance Mutations Group is building an online database of references (peer-reviewed, published articles, and conference abstracts) that will provide state-of-the-art information on the effect of mutations on drug susceptibility, the interactions between mutations, and the impact of drug levels on the effects of specific mutations in clinical settings. For each mutation or mutation pattern marked in the mutations figures, the database will include findings from the scientific literature that demonstrate clinical impact. Users will be able to search by mutation, class of drug, study type, authors, and other key aspects.

The launch of this database will be announced in *Topics in* HIV *Medicine* and at www.iasusa.org. Comments on the current mutations figures can be addressed via e-mail to info@iasusa.org.

The Drug Resistance Mutations Group

The current members of the Drug Resistance Mutations Group are:

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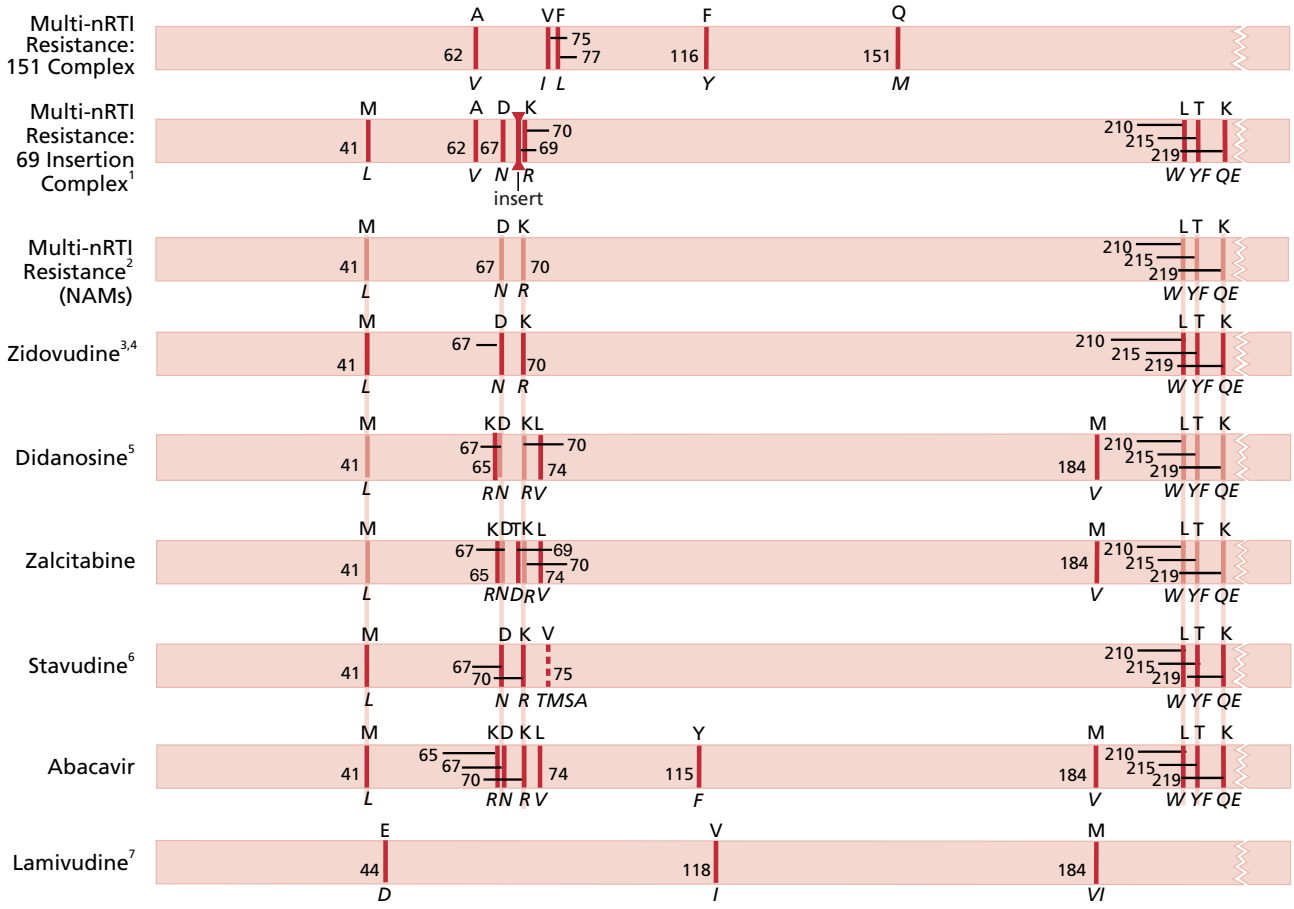
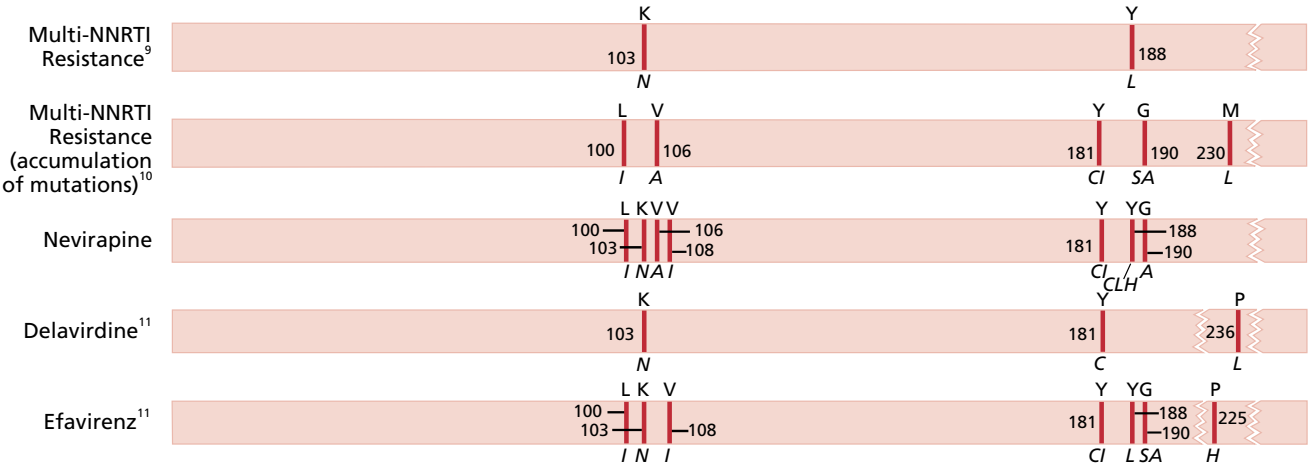
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside Reverse Transcriptase Inhibitors



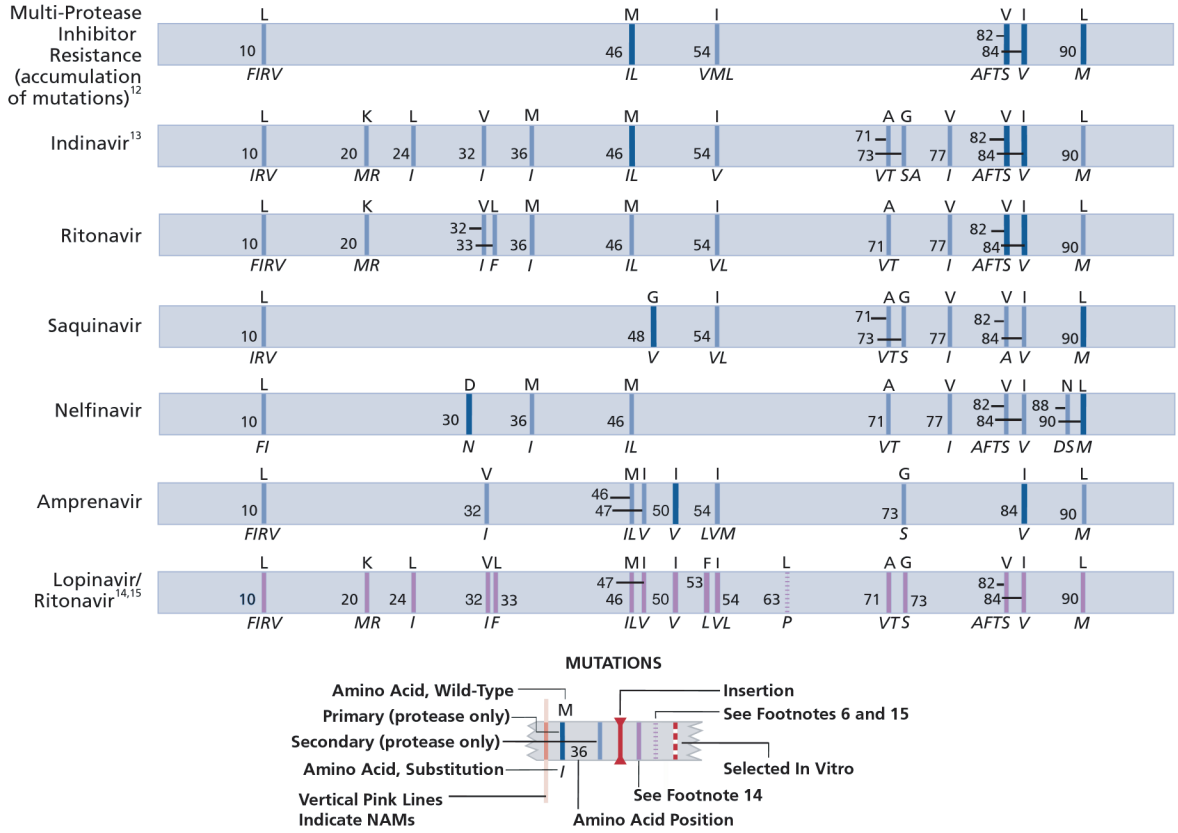
Nucleotide Reverse Transcriptase Inhibitor

Nonnucleoside Reverse Transcriptase Inhibitors



MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO PROTEASE INHIBITORS

Protease Inhibitors



For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the italicized letter(s) below indicates the substitution(s) that confer viral resistance. The number shows the position of the mutation in the protein. Mutations selected by protease inhibitors in Gag cleavage sites are not listed because their contribution to resistance is not yet fully defined. NAMs indicates multi-nRTI-associated mutations; nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor. The figures are adapted in part from Hirsch et al, JAMA, 2000, and are updated regularly. Date of last revision: November 15, 2001.

Amino acid abbreviations are: *A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.*

Footnotes

[1]The 69 insertion complex, consisting of a mutation at codon 69 (typically T69S) and followed by an insertion of 2 or more amino acids (S-S, S-A, S-G, or others), is associated with resistance to several nRTIs. The 69 insertion is often accompanied by mutations at other sites. Some other amino acid changes from the wild-type T in codon 69 without the insertion may also be associated with broad nRTI resistance.

[2]Multi-nRTI-associated mutations (NAMs): mutations associated with cross-resistance to nRTIs (except lamivudine).

[3]Reverse transcriptase mutation M184V may temporarily partially reverse the effects of the mutations shown here on zidovudine susceptibility. However, if more than 3 of the listed mutations are present, the additional presence of M184V is not likely to reverse phenotypic zidovudine resistance.

[4]The D/C/S substitutions in RT codon 215 do not confer zidovudine resistance, and suggest that virus evolved from the zidovudine-resistant mutant T215Y to a variant that is more fit in the absence of drug. In vitro studies indicate that 215Y may emerge quickly from 215D/C/S in the presence of drug; in vivo relevance is possible but not yet proven.

[5]One of the following (K65R; L74V) by itself OR a combination of a few of the following (NAMs, E44D, T69D/N, V118I) can lead to didanosine resistance.

[6]V75 T/M/S/A are seldom observed in patients in whom stavudine has failed.

[7]One article reports that E44D and/or V118I mutations confer low-level resistance to lamivudine when accompanied by several of the NAMs (41L, 67N, 210W, 215Y/F, 219Q/E), in the absence of a concurrent M184V mutation (Hertogs et al, *Antimicrob Agents Chemother*, 2000). One abstract (D'Arminio-Monforte et al, 8th Conference on Retroviruses and Opportunistic Infections, 2001, Chicago, Abstract 447) reported no association over the short term between E44D or V118I and viral load responses to a lamivudine-containing combination regimen.

[8]In vitro data suggest that 4 or more NAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) will lead to a significant degree of resistance; the actual clinical cut-off for tenofovir DF IC_{50} or a detailed relationship between specific multiple NAMs and tenofovir DF IC_{50} has not yet been published. Clinical trial results presented by Gilead to the FDA Advisory Committee in September 2001 (unpublished) indicate reduced viral load responses to tenofovir DF in groups of patients in whose plasma virus 3 or more NAMs including either M41L or L210W were identified. The group of patients with plasma virus in which any accumulation of D67N, K70R, T215Y/F, or K219Q/E were identified (in the absence of detection of M41L or L210W) did not have a diminished average HIV RNA response to tenofovir DF in that dataset.

[9]The K103N or Y188L mutation by itself can substantially reduce the clinical utility of all currently approved NNRTIs.

[10]Accumulation of these mutations (2 or more) substantially reduces the clinical utility of all of the currently approved NNRTIs.

[11]There are some in vitro data suggesting that the Y318F mutation, alone or in the presence of K103N and Y181C, decreased susceptibility to delavirdine in primary HIV infection. This mutation was observed only rarely in clinical isolates. An effect of the Y318F mutation on efavirenz susceptibility in vitro was detected if the K103N mutation was also present. However, confirmatory data and/or analyses in clinical HIV infection are needed to confirm clinical relevance.

[12]Accumulation of these mutations (4 or 5 or more) will likely cause multi-protease inhibitor resistance.

[13]For indinavir, the mutations listed as primary may not be the first mutations selected, but they are present in most patient isolates in combination with other mutations.

[14]"Primary" mutations versus "secondary" mutations have not been designated for lopinavir/ritonavir-associated resistance since there are currently no clear data defining which mutation(s) is(are) selected first with this drug combination. The accumulation of 6 or more of these mutations is associated with a diminished response to lopinavir/ritonavir. The accumulation of 7 or 8 or more of these mutations makes a response to lopinavir/ritonavir unlikely. The mutations listed are based on one report (Kempf et al, 4th International Workshop on HIV Drug Resistance and Treatment Strategies, 2000, Sitges, Spain, Abstract 89). Further clinical experience and research are needed to better define the mutations that affect the effectiveness of lopinavir/ritonavir.

[15]Protease mutation L63P is common in viruses that have never been exposed to protease inhibitors (Kozal et al, *Nat Med*, 1996), and may be more prevalent in viruses from patients in whom a protease inhibitor-containing regimen has failed. However, by itself, protease mutation L63P does not cause any appreciable increase in the IC_{50} for any protease inhibitor. L63P is listed for lopinavir/ritonavir (and not any other protease inhibitor) because the prescribing information approved by the US Food and Drug Administration lists it as one of the numerous mutations that together predict a lack of viral load response to lopinavir/ritonavir-containing regimens.

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HIV/AIDS Practitioners

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Symposia Faculty

IAS–USA symposia this year included the ninth annual winter/spring series, *Improving the Management of* HIV *Disease*: HIV *Pathogenesis, Antiretrovirals, and Other Selected Issues in* HIV *Disease Management*; the seventh annual fall series, *Current Challenges in* HIV *Disease*: A *Case-Based, Advanced Course in Clinical* HIV *Management*; and the *4th Annual* HIV *Clinical Conference* for Ryan White CARE Act Title III and IV providers.

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Antiretroviral Therapy Guidelines Panel

The Antiretroviral Therapy Panel published its first set of guidelines in 1996; the next recommendations will be submitted for publication in 2002.

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Resistance Testing Guidelines Panel

The Resistance Testing Panel published its second set of recommendations in JAMA in May 2000, and a revised report is in development.

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Drug Resistance Mutations Group

The Mutations Group was convened in 2000 to maintain an ongoing, up-to-date database of HIV drug resistance mutations reflecting current research in the field. The panel issued several updates of its list of mutations in 2001; the most recent update is published in this issue of *Topics in* HIV *Medicine* and is also available at www.iasusa.org.

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Metabolic Complications Panel

The Metabolic Complications Panel was convened in 2000 and submitted recommendations for publication in 2001.

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[1]International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2001. Available at http://www.icmje.org. Accessed November 1, 2001.

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Established in 1992, the International AIDS Society–USA is a not-for-profit physician education organization. The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the-art education and information for physicians who are actively involved in HIV and AIDS care. The organization's educational activities are particularly intended to bridge clinical research and patient care.

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