Perspectives

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

Dr Benson is Professor of Medicine, Division of Infectious Diseases, at the University of Colorado Health Sciences Center in Denver.

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.

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, N*ature*, 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 expo-

sure 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
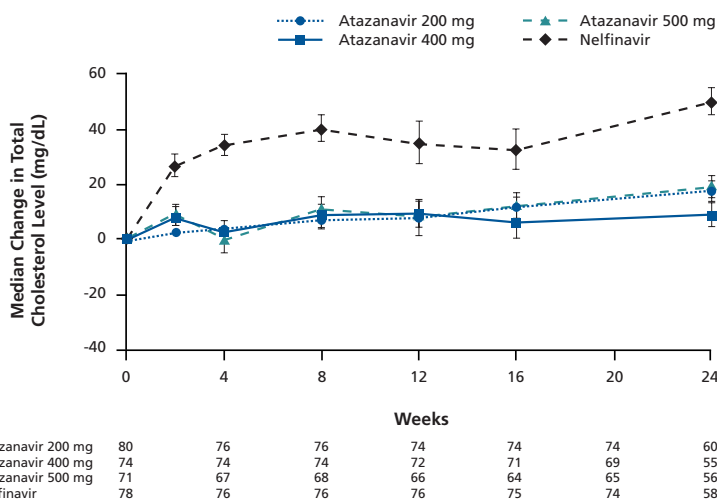

Atazanavir 200 mg	80	76	76	74	74	74	60
Atazanavir 400 mg	74	74	74	72	71	69	55
Atazanavir 500 mg	71	67	68	66	64	65	56
Nelfinavir	78	76	76	76	75	74	58

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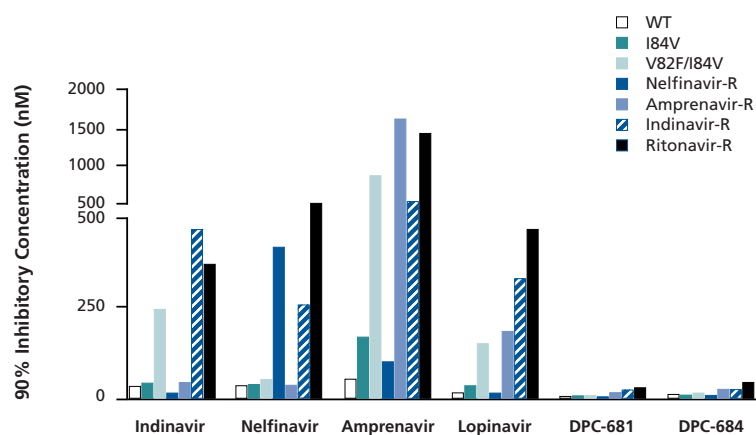
Figure 2. Ninety percent inhibitory concentrations of DPC-681 and DPC-684 and other protease inhibitors against wild-type (WT) virus and protease inhibitor-resistant (R) virus. Adapted with permission from Erickson-Viitanen et al, 8th CROI, 2001.

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 indi-

navir, 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

Bacheler LT, Jeffrey S, Logue K, et al. Resistance profiles of second generation HIV protease inhibitors DPC 681 and DPC 684. [Abstract 6.] *Antivir Ther*. 2001;6(suppl 1):5.

Buckheit RW, Turpin JA, Pallansch LA, et al. Antiviral resistance and mechanism of action of SJ-3366, a novel non-nucleoside inhibitor of HIV-1 and HIV-2 with two distinct mechanisms of action. [Abstract 13.] *Antivir Ther*. 2001;6(suppl 1):10.

Curry R, Markowitz M, Slater L, Neubacher D, Robinson P, Cotton G. Safety and efficacy of tipranavir, a non-peptidic protease inhibitor, in multiple PI-failure patients (BI 1182.2). 1st International AIDS Society Conference on HIV Pathogenesis and Treatment. July 7-11, 2001; Buenos Aires, Argentina.

de Béthune MP, Azijn H, Andries K, Janssen P, Pauwels R. In vitro selection experiments demonstrate reduced development of resistance with TMC120 and TMC125 compared with first generation non-nucleoside reverse transcriptase inhibitors. [Abstract 7.] *Antivir Ther*. 2001;6(suppl 1):6.

Dybul M, Chun TW, Yoder C, et al. Short-cycle intermittent HAART: a pilot study. [Abstract 354.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Erickson J, Gulnik S, Suvorov L, et al. A femtomolar HIV-1 protease inhibitor with sub-nanomolar activity against multidrug resistant HIV-1 strains. [Abstract 12.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Erickson-Viitanen S, Kaltenbach R, Getman D, et al. DPC 681 and DPC 684: resistance and cross-resistance profiles of second generation HIV protease inhibitors. [Abstract 11.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Eron J, Merigan T, Kilby M, et al. A 14-day assessment of the safety, pharmacokinetics, and antiviral activity of T-129, a peptide inhibitor of membrane fusion. [Abstract 14.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Fagard C, Lebraz M, Gunthard H, et al. SSITT: a prospective trial of strategic treatment interruptions in 128 patients. [Abstract 357.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Fauci A. Host factors in the pathogenesis of HIV disease: implications for therapeutic strategies. [Abstract PL4.] 1st International AIDS Society Conference on HIV Pathogenesis and Treatment. July 7-11, 2001; Buenos Aires, Argentina.

Garcia F, Plana M, Ortiz GM, et al. The virological and immunological consequences of structured treatment interruptions in chronic HIV-1 infection. AIDS. 2001;15:F29-F40.

Gruzdev B, Horban A, Boron-Kaczmarska A, Gille D, Van't Klooster G, Pauwels R. TMC120, a new non-nucleoside reverse transcriptase inhibitor, is a potent antiretroviral in treatment naive, HIV-1 infected subjects. [Abstract 13.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Gruzdev B, Rakhmanova A, De Dier K, Comhaire S, Baede-Van Dijk P, Van'T Klooster G. TMC125 is a highly potent non-nucleoside reverse transcriptase inhibitor (NNRTI) in antiretroviral therapy (ART)-naive, HIV-1 infected subjects. [Abstract P668.] 41th Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001; Chicago, Ill.

Hazuda D, Schleif W, Gabryelski L, et al. Resistance to integration inhibitors: evolution of active site mutations, relationship to fitness and enzyme co-factor utilization. [Abstract 9.] *Antivir Ther*. 2001;6(suppl 1):7

Larder BA, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS. 2000;14:1943-1948.

Martinez-Picado J, Morales-Lopetegi K, Wrin T, et al. Selection of the M184V mutation during repetitive cycles of structured antiretroviral treatment interruptions. [Abstract 36.] *Antivir Ther*. 2001;6(suppl 1):28.

Miralles GD, DeMasi R, Sista P, Melby T, Duff F, Matthews T. Baseline genotype and prior antiretroviral history do not affect virological response to T-1249. [Abstract 3.] *Antivir Ther*. 2001;6(suppl 1):4.

Miro JM, Plana M, Ortiz GM, et al. Structured treatment interruptions (STI) in patients receiving HAART since primary HIV-1 infection (PHI): spontaneous control of viremia in almost half of cases after the first two cycles off therapy. [Abstract P1908.] 41th Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001; Chicago, Ill.

Parish MA, Raines C, Higgins M, Gallant JE. Treatment discontinuation (DC) in patients with marginal indications for HAART. [Abstract P673.] 41th Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001; Chicago, Ill.

Rosenberg ES, Altfeld M, Poon SH, et al. Immune control of HIV-1 after early treatment of acute infection. *Nature*. 2000;407:523-526.

Ruiz L, Carcelain G, Martinez-Picado J, et al. HIV dynamics and T-cell immunity after three structured treatment interruptions in chronic HIV-1 infection. AIDS. 2001;15:F19-F27.

Sierra-Madero J. Antiviral activity, safety and pharmacokinetics of mozenavir (CMP 450), a novel cyclic urea protease inhibitor, in combination with d4T and 3TC in treatment-naive HIV-1 infected patients (Study DMP-102). 1st International AIDS Society Conference on HIV Pathogenesis and Treatment. July 7-11, 2001; Buenos Aires, Argentina.

Squires K, Gatell J, Piliero P, Sanne I, Wood R, Schnittman SM. AI424-007: 48-week safety and efficacy results from a phase II study of a once-daily HIV-1 protease inhibitor (PI), BMS-232632. [Abstract 15.] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001; Chicago, Ill.

Tebas P, Henry K, Mondy K, et al. Effects of prolonged discontinuation of successful antiretroviral therapy. [Abstract 31.] 1st IAS Conference on HIV Pathogenesis and Treatment. July 7-11, 2001; Buenos Aires, Argentina.

Tremblay C, Hicks J, Sutton L, et al. HIV evolution during repeated supervised treatment interruptions following early antiretroviral treatment of acute infection. [Abstract 18.] *Antivir Ther*. 2001;6(suppl 1):17.

van der Geest R, Van der Sandt I, Gille D, Groen K, Tritsmans L, Stoffels P. Safety, tolerability and pharmacokinetics of escalating single oral doses of TMC114, a novel protease inhibitor (PI) highly active against HIV-1 variants resistant to other PIs. [Abstract P1934.] 41th Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001; Chicago, Ill.