Perspectives

Investigational Drugs in HIV Therapy: Review of Select New Antiretrovirals

Martin S. Hirsch, MD

New antiretroviral drugs at various stages of investigation and development were reviewed by Martin S. Hirsch, MD, at the Boston course in March.

Optimal HIV-1 suppression often is difficult to achieve and maintain with currently available antiretroviral drugs, and viral resistance eventually emerges to many drugs. Chronic antiretroviral therapy is also associated with complications such as body fat redistribution, hypertriglyceridemia and hypercholesterolemia, abnormal glucose metabolism, lactic acidosis, pancreatitis, avascular necrosis of bone, and osteoporosis. New drugs are needed to enhance anti-HIV potency, overcome viral resistance, increase tolerability and convenience, and reduce toxicity. A number of antiretroviral drugs are in development, including new nucleotide reverse transcriptase inhibitors (*nt*RTIs), nucleoside reverse transcriptase inhibitors (nRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion and coreceptor inhibitors, and integrase inhibitors. This selective review will summarize some of the more promising compounds under study.

Nucleotide Reverse Transcriptase Inhibitors

Tenofovir

Tenofovir disoproxil fumarate is an investigational analogue of dAMP that does not require initial phosphorylation by viral kinases. Its predecessor adefovir is no longer being developed for HIV therapy because of concerns related to antiviral activity and renal toxicity. Tenofovir exhibits a half-life that permits once-daily dosing and has potent in vitro activity against HIV (and simian immunodeficiency virus [SIV]), including activity against nRTI-resistant HIV and multidrug-resistant virus with the Q151M mutation.

In a short-term clinical study, tenofovir produced a clear dose-response in viral load reduction. Although viral load decreased by approximately 1.5 log in treatment-naive patients, the decrease was smaller in treatment-experienced patients. In a subsequent study, treatment-experienced patients with at least 8 weeks of stable potent therapy (mean, 4.6 years of therapy), viral load of 400 to 100,000 HIV RNA copies/mL, and adequate renal function had tenofovir at 75, 150, or 300 mg or placebo added to their current regimen. In this study, 85% of patients had zidovudine-resistant virus, most with multiple mutations, and 67% had the lamivudine-associated M184V resistance mutation. As shown in Figure 1, dose-related decreases in viral load were observed, with a maximum decrease of approximately 0.8 log with the highest dose. A similar response was observed in the initial placebo group when tenofovir was added at 24 weeks.

Resistance to tenofovir can be generated in vitro by a K65R mutation, but thus far this mutation appears to be uncommon in tenofovir-treated patients. The insertion mutations at positions 69 and 70 of RT that are associated with multi-nRTI resistance confer cross-resistance to tenofovir. Although available clinical data on tenofovir use thus far extend only to the 24- to 72-week period, significant nephrotoxicity has not been observed to date; adefovir-associated nephrotoxicity was commonly observed within this time frame. Phase III trials of tenofovir are in progress. A limited expanded access program has been conducted for patients with advanced disease, but is no longer open to enrollment.

Nucleoside Reverse Transcriptase Inhibitors

Emtricitabine

Emtricitabine (FTC) is a highly active oxathiolane nucleoside analogue with potency against HIV and hepatitis B virus (HBV) in vitro. Its structure differs from that of lamivudine only in the presence of a fluoride residue at position 5 on the pyrimidine ring. Emtricitabine is 4- to 10-times more potent than lamivudine in vitro (in some systems) and is synergistic with a broad range of nRTIs, NNRTIs, and

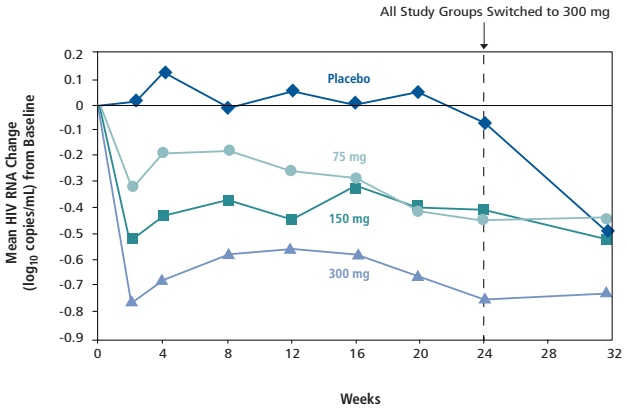

Figure **1.** Mean change in plasma viral load according to tenofovir dose group in study 902 in treatment-experienced patients. Courtesy of Ian McGowan, MD, PhD, Gilead Sciences, Foster City, Calif.

Dr Hirsch is Professor of Medicine at Harvard Medical School and Director of Clinical AIDS Research at the Massachusetts General Hospital in Boston. Dr Hirsch is also a member of the International AIDS Society–USA Antiretroviral Therapy Guidelines Panel and the chair of the organization's panel on guidelines for the clinical use of resistance testing in antiretroviral management.

protease inhibitors. Plasma and intracellular pharmacokinetics support once-daily dosing of the drug, with high intracellular levels of the triphosphate form being dose-related (apparent saturation at doses >200 mg). In early clinical studies, administration of doses of 200 mg or higher was associated with 1.72- to 1.92-log decreases in viral load. Clinical studies assessing once-daily dosing are under way.

DAPD

Diaminopurine dioxolane (DAPD), which is converted in vivo to the dioxolane guanine analogue DXG, also exhibits activity against HIV and HBV. The pharmacokinetics of the drug support once- or twice-daily dosing. DAPD retains activity against zidovudine- and lamivudine-resistant mutants, and is active against some virus with codon 69 mutations conferring multi-nRTI resistance. Virus with the K103N mutation associated with NNRTI resistance may exhibit hypersensitivity to DAPD. Resistance to DAPD is selected in vitro by K65R and L74V mutations. Once-daily and twice-daily dose schedules currently are being assessed in Phase I/II studies. Marked short-term activity has been observed in treatment-naive patients, with 14-day data indicating viral load decreases of 1.5 to 2 log; treatment-experienced patients currently are being enrolled in the early phase studies.

Nonnucleoside Reverse Transcriptase Inhibitors

Capravirine

Capravirine (Ag1549) retains activity in vitro against virus with some of the single-point mutations characteristic of NNRTI resistance, including the K103N mutation associated with resistance to currently approved NNRTIs. It also exhibits activity, albeit reduced, against some HIV isolates with more than one NNRTI resistance mutation. High-level resistance to the drug requires more than one mutation; concomitant V106A and F227L mutations are associated with a more than 380-fold increase in 50% inhibitory concentration (IC_{50}). In testing of doses of up to 2100 mg twice daily in NNRTI-naive patients, viral load was reduced by 1.7 log over 10 to 28 days, with minimal toxicity (primarily diarrhea and nausea) being observed. Coadministration with nelfinavir results in a 5-fold increase in the minimum concentration of capravirine. Phase II and III studies of capravirine have been initiated.

Protease Inhibitors

Lopinavir

Lopinavir (ABT-378/r) is a combination of ritonavir and ABT-378, an investigational protease inhibitor structurally related to ritonavir. ABT-378 exhibits 10-fold greater in vitro activity against HIV and retains activity against HIV with the codon 82 mutation characteristic of initial resistance to ritonavir and indinavir. It is also more active than ritonavir against virus with numerous ritonavir resistance mutations. Each tablet of lopinavir contains 133.3 mg of ABT-378 and 33.3 mg of ritonavir. Plasma levels of ABT-378 are dramatically increased by coadministration of low doses of ritonavir, permitting twice-daily dosing.

Lopinavir has been assessed in treatment-naive and treatment-experienced patients. In the M97-720 study, 100 treatment-naive patients received ABT-378/r 200/100 mg (respectively) or 400/100 mg twice daily alone for 3 weeks. This was followed by the addition of stavudine/lamivudine (Group 1) or ABT-378/r (400/100 mg or 400/200 mg bid) together with stavudine/lamivudine from study day 1 (Group 2). All patients converted to open-label lopinavir 400/100 mg twice daily plus the other 2 drugs at week 48. More than 90% of patients had viral load decreases to below 400 copies/mL at 72 weeks in on-treatment analysis. The most common adverse events were diarrhea (19% and 22% in Groups 1 and 2, respectively), nausea (6% and 19%), and abnormal stools (19% and 3%). Elevations of total cholesterol or triglyceride levels were observed in 12% to 15% of patients respectively in the 2 groups.

In Study M97-765, 70 patients who had been receiving a protease inhibitor and 2 nRTIs for at least 3 months and had single protease inhibitor failure with viral loads of 1000 to 100,000 copies/mL received ABT-378/r 400/100 mg or 400/200 mg twice daily. Nevirapine was added and the nRTIs were changed to include at least 1 new drug at day 15. Viral load was reduced to below 400 copies/mL in 84% of patients at week 24 in on-treatment analysis. The mean increase in CD4+ cell count was 125/μL at week 48. This degree of activity in treatment-experienced patients appears to be related to the ability of this combination at either study dose to maintain plasma ABT-378 concentrations exceeding the 50% effective concentration (EC_{50}) for virus in these patients (Figure 2). Lopinavir currently is being evaluated in a Phase II study in patients with multiple protease inhibitor experience.

Phase III pivotal studies of lopinavir are under way. It currently is also available in an expanded access program limited to patients with advanced HIV disease, and criteria for wider availability are in development.

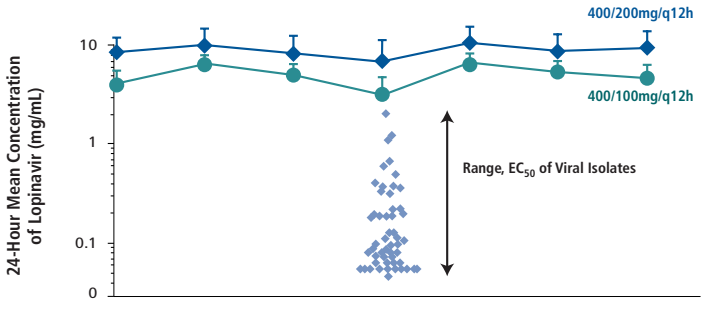

Figure **2.** Lopinavir 24-hour mean concentrations at study dosages and 50% effective concentrations (EC_{50}) for HIV isolates (adjusted for 50% serum) in study M97-765. Courtesy of Eugene Sun, Abbott Laboratories, Abbott Park, Ill.

Tipranavir

Tipranavir is a nonpeptide drug that exhibits broad activity against protease inhibitor-resistant variants. A study of 107 highly protease inhibitor-resistant clinical virus variants (>10-fold reduction in susceptibility to 3 or more drugs) showed that 90% were susceptible to tipranavir. Some variants were hypersensitive to the drug and only 3% had more than 10-fold reduction in susceptibility. In vitro resistance to tipranavir is associated with the 82T/84V

Table 1. Early Phase Study of a Pentafuside-Containing Multidrug Salvage Regimen

Patients/ Drug History	55 patients/Used a median of 11 prior antiretrovirals (93% with exposure to 3 drug classes)
Median Baseline CD4+ Count	70 cells/mL
Median Baseline HIV RNA	4.9 $\log_{10}$ copies/mL
At 16 weeks, no. of patients with:	
HIV RNA >1 $\log_{10}$ below baseline or with <400 copies/mL at 16 weeks	33 of 55 (60%)
<400 copies/mL	20 of 55 (36%)

Adapted from Lalezari et al, 39th ICAAC, 1999.

and 84V/90M mutations, but these mutations have not been consistently observed.

Development of tipranavir has been hindered by formulation problems and rapid metabolism by the cytochrome P450 3A4 isoenzyme. Initial studies indicated that the drug was associated with a modest 1.0- to 1.5-log decrease in viral load over 28 days with 1500 mg 3 times a day; it appears that adherence to the study regimen was poor due to the number of pills required. A new formulation currently is being evaluated, and it has been shown that trough concentrations of the drug are increased 7- to 40-fold by coadministered ritonavir, allowing twice-daily dosing of the drug. Phase II studies of the new formulation of tipranavir combined with ritonavir (1200/200 mg bid, respectively) in treatment-naive patients are in progress.

BMS 232,632

BMS 232,632 is an azapeptide drug with activity against variants resistant to nelfinavir and saquinavir and partial activity against indinavir- and ritonavir-resistant virus. It is suspected to have a resistance pathway unique among protease inhibitors. Bioavailability of the drug is 53% to 72% and the terminal half-life is 3 to 7 hours, suggesting that once-daily dosing may provide adequate minimum concentrations. The drug also exhibits favorable pharmacokinetics in combination with saquinavir. Phase II studies of BMS 232,632 are in progress, including evaluation of short-term activity of once-daily monotherapy and longer-term activity of combinations with 2 nRTIs in treatment-naive patients and of once-daily administration in combination with saquinavir in protease inhibitor-experienced patients.

Fusion Inhibitors

Pentafuside

Pentafuside (T-20), a 36-amino acid peptide, is a specific and potent inhibitor of gp41-mediated fusion of HIV with the host cell membrane. It does not exhibit cross-resistance to other current antiretrovirals and has a synergistic effect in vitro with several reverse transcriptase inhibitors and protease inhibitors. The drug must be administered parenterally and is currently being evaluated using a twice-daily subcutaneous injection regimen. In an early-phase study, pentafuside treatment was associated with a 1.5- to 2.0-log decrease in viral load and a mean increase in CD4+ cell count of 215/µL over 32 weeks in treatment-experienced patients. Sixteen-week data are presented in Table 1. Systemic toxicity with the drug has been infrequent. Resistant isolates have been obtained in vitro and resistance in vivo has been observed after prolonged therapy in association with mutations in HIV gp41. Pentafuside currently is in Phase II trials.

T-1249

T-1249, a 39-amino acid hybrid peptide of HIV-1, HIV-2, and SIV, was designed to bind to a different gp41 region than pentafuside. It is 2- to 100-times more active in vitro than pentafuside and is highly active against pentafuside-resistant HIV. The drug was designed to provide improved pharmacokinetics, and Phase I/II dose-escalating trials including once-daily parenteral administration are under way.

Although pentafuside and T-1249 may prove to be of clinical utility, the need for long-term subcutaneous administration is a drawback. Orally available fusion inhibitors directed at the same target are under development.

Drugs Acting on Other Targets

Coreceptor Blockers

Other drugs in development that act at the viral attachment or entry stage include blockers of the HIV coreceptors CCR5 (AOP-RANTES and Schering-C) and CXCR4 (AMD3100 and T140). Studies in vitro have shown that the combination of pentafuside and the CXCR4 blocker AMD3100 is strongly synergistic against lymphotropic (X4) viral isolates, indicating that targeting of sequential steps in attachment or entry may be a useful strategy. Clinical activity of coreceptor blocker compounds has yet to be demonstrated.

Integrase Inhibitors

The HIV integrase is responsible for inserting proviral DNA into the host cell genome. This enzyme, for which there is no known cellular homologue, is conserved in all retroviruses and is required for stable maintenance of the viral genome and efficient viral gene expression. Much work has been done over the past several years in the attempt to develop integrase inhibitors. Progress has been slowed by the difficulty inherent in the in vitro study of the multistep process culminating in integration of the proviral DNA. Inhibitor molecules identified in this research have been primarily DNA-binding compounds that prevent assembly of the viral preintegration complex. These inhibitors are relatively nonspecific for HIV integrase and exhibit poor antiretroviral activity in tissue culture.

However, a recent report indicates the development of a class of integrase inhibitors that bind to the preintegration complex and inhibit the strand-transfer reaction in integration. These molecules exhibit potent inhibition of HIV replication in tissue culture; their activity against HIV integrase is indicated by the development of resistance mutations mapping to the integrase *int* region of the HIV *pol* gene with

serial passage of virus in the presence of the inhibitors. Candidate molecules in this class currently are undergoing modification to generate clinically useful compounds.

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