

Perspective

Current Status of New Antiretroviral Drugs in Development

At the International AIDS Society–USA course in Washington, DC, in May 2002, Roy M. Gulick, MD, MPH, discussed characteristics of select investigational antiretroviral drugs, including new reverse transcriptase and protease inhibitors and drugs that inhibit HIV entry and integration.

Currently, 16 antiretroviral drugs are approved for treatment of HIV infection. However, even the best currently available regimens pose challenges with regard to adherence, toxicity, antiviral activity, and resistance. New drug development thus confronts the need for improved convenience and tolerability, reduced toxicity, and improved activity against both wild-type and drug-resistant viruses. Other goals of drug development include improved drug penetration into viral reservoirs (eg, genital tract and central nervous system) and exploitation of additional viral targets with the aims of achieving additive or synergistic effects with drugs from existing classes, reducing or preventing viral resistance, and improving treatment options in cases of drug resistance.

Newly available or investigational formulations or doses of existing nucleoside reverse transcriptase inhibitors (nRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) are shown in Table 1. Selected investigational drugs in existing and new drug classes are shown in Table 2; select drugs from this listing are discussed herein. Figures 1 and 2 show the HIV-1 life cycle and the stages of the life cycle targeted by available drug classes and by drugs from newer and investigational classes such as entry inhibitors and integrase inhibitors.

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HIV Nucleoside Reverse Transcriptase Inhibitors

Amdoxovir

Amdoxovir (DAPD) is an investigational guanine analogue active in vitro against both HIV and hepatitis B virus. Pharmacokinetic data support twice-daily dosing of the compound. Amdoxovir is active in vitro against zidovudine-resistant and lamivudine-resistant virus and some multidrug-resistant strains with the reverse transcriptase codon 69 insertion. The reverse transcriptase mutations K65R and L74V reduce susceptibility to the compound in vitro. The K103N mutation associated with efavirenz resistance may be associated with hypersensitivity to amdoxovir. In animal toxicity studies, the compound produced an obstructive nephropathy, caused by crystallization of the compound in the renal tubules, that led to hyperglycemia and cataracts in some animals.

In an initial study in 24 patients who had received prior zidovudine or stavudine and prior lamivudine, amdoxovir was given at 200 mg, 300 mg, or 500 mg twice daily after drug washout or at 500 mg twice daily in addition to the patients' current regimen (Raffi et al, 5th Int Cong Drug Ther HIV Infect, 2000). In patients undergoing drug washout, amdoxovir 500 mg twice daily reduced plasma HIV-1 RNA level by a median of 1 log₁₀ copies/mL at 15 days, with smaller reductions observed at lower doses. The addition (without washout) of amdoxovir to background treatment produced a median 2-log₁₀ decrease in plasma HIV-1 RNA level, although the reason for this greater decrease is not clear. Mycophenolic acid inhibits inosine 5'-monophosphate dehydrogenase and thereby depletes intracellular dGTP levels, thus enhancing the in vitro antiviral activity of guanosine nucleoside analogues such as abacavir and amdoxovir

(Margolis et al, *J Acquir Immune Defic Syndr Hum Retrovirol*, 1999; Ying et al, *Antiviral Res*, 2000). Phase 2 studies of amdoxovir, both with and without mycophenolic acid, are in progress.

HIV Nonnucleoside Reverse Transcriptase Inhibitors

BMS 56,1390 (DPC-083)

A number of NNRTIs that are structurally related to efavirenz have been developed, and the leading clinical candidate

Table 1. New Formulations and Dosing Strategies of Existing Antiretroviral Drugs

HIV Nucleoside Reverse Transcriptase Inhibitors

- zidovudine bid dosing*; controlled-release formulation qd
- didanosine enteric-coated capsule qd*
- zalcitabine bid
- stavudine extended release 100 mg qd
- lamivudine qd*
- lamivudine/zidovudine fixed-dose combination*
- lamivudine/zidovudine/abacavir fixed-dose combination*
- lamivudine/abacavir fixed-dose combination

HIV Nonnucleoside Reverse Transcriptase Inhibitors

- delavirdine 200-mg tablet*
- efavirenz 600-mg capsule*

HIV Protease Inhibitors

- saquinavir soft-gel formulation*; 800-mg hard-gel capsule
- nelfinavir bid dosing*; 625-mg tablet
- ritonavir enhancement of saquinavir, indinavir, or amprenavir*
- lopinavir/ritonavir coformulation*
- GW433908 (amprenavir prodrug VX-175)

* Currently approved by the US Food and Drug Administration.

is BMS 56,1390 (formerly DPC-083). This compound exhibits good oral bioavailability and has a half-life of greater than 90 hours, supporting once-daily and perhaps less frequent dosing. The compound undergoes metabolism via the cytochrome P450 (CYP) 3A4 and 2B6 hepatic isoenzyme systems. Compared with efavirenz, BMS 56,1390 exhibits 3-fold greater activity in vitro against K103N mutants and some double mutants. Resistance in vitro appears to require the presence of more than 1 reverse transcriptase mutation. The compound currently is in phase 2 and 3 evaluation.

In a recently reported study, 134 treatment-naive patients with an average plasma HIV-1 RNA level of 33,000 copies/mL and CD4+ cell count of 402/ μ L received fixed-dose lamivudine/zidovudine at the standard dose plus efavirenz 600 mg or BMS 56,1390 at 50-mg, 100-mg, or 200-mg once-daily doses. In an intent-to-treat analysis, 60% to 70% of patients in the 4 arms had plasma HIV-1 RNA level reduced to less than 50 copies/mL at 16 weeks (Ruiz et al, Abstract 7, 9th CROI, 2002).

In another study, 75 NNRTI-experienced/PI-naive patients in whom current therapy was failing received 2 nRTIs selected on the basis of genotypic analysis and BMS 56,1390 at 100 mg or 200 mg once daily (Ruiz et al, Abstract 6, 9th CROI, 2002). At baseline, patients had an average plasma HIV-1 RNA level of 6900 copies/mL and a CD4+ cell count of 518/ μ L; 61% had received prior nevirapine and 39% had received prior efavirenz. A total of 31% of patients discontinued study treatment early. In most cases, discontinuation was due to violation of study protocol by prior receipt of PI treatment. Approximately 40% to 50% of all patients had a plasma HIV-1 RNA level less than 400 copies/mL at 16 weeks in an intent-to-treat analysis. Unexpectedly, adverse effects were more common in patients receiving the 100-mg dose of BMS 56,1390 than in those receiving the 200-mg dose. Rash was observed in the 100-mg group but not in the 200-mg group; other adverse effects included headache and somnolence. No decision regarding the dose of the compound to be employed in subsequent clinical evaluation could be made on the basis of this study.

Table 2. Selected Investigational Antiretroviral Drugs

HIV nRTIs

- ACH-126,443 (L-Fd4C)
- alovedine (FLT, MIV-310)
- amdoxovir (DAPD)
- D-FDOC
- DPC 817 (D-d4FC)
- emtricitabine (FTC)
- SPD 754
- SPD 756 (BCH-13520)

HIV NNRTIs

- BMS 56,1390 (formerly DPC-083)
- calanolide A
- capravirine (Ag-1549)
- HBY 1293
- MIV-150
- SJ-3366
- TMC 125

HIV Protease Inhibitors

- atazanavir (BMS 232632)
- mozenavir (DMP-450)
- tipranavir
- TMC 114

HIV nRTIs

- GS 7340

HIV Entry Inhibitors

- CD4 attachment inhibitors
 - BMS-806
 - PRO 542
- Coreceptor inhibitors
 - CXCR4 inhibitors
 - AMD-3100*
 - AMD-070
 - CCR5 inhibitors
 - PRO 140
 - SCH-C (SC-351125)
 - SCH-D
 - UK-427,857
- Fusion inhibitors
 - enfuvirtide (T-20)
 - T-1249

HIV Integrase Inhibitors

- L-870810
- S-1360

Other

- PA-344b (double-stranded DNA production inhibitor)
- PA-457 (maturation/budding inhibitor)

NNRTIs indicates nonnucleoside reverse transcriptase inhibitors; nRTIs, nucleoside reverse transcriptase inhibitors; nRTIs, nucleotide reverse transcriptase inhibitors. *Clinical development discontinued.

TMC 125

TMC 125 is an investigational NNRTI that exhibits antiretroviral activity in vitro against a high proportion of clinical HIV isolates with resistance to nevirapine, delavirdine, or efavirenz. In a study in treatment-naive, HIV-infected patients with an average baseline HIV-1 RNA level of 58,000 copies/mL and CD4+ count of 650 cells/ μ L, TMC 125 900 mg twice daily given as monotherapy produced a 2- \log_{10} reduction in plasma HIV-1 RNA level in 12 patients at 7 days, compared with no change in 7 placebo recipients (Gruzdev et al, 41st ICAAC, 2001). In a study in 16 NNRTI-experienced patients (prior nevirapine in 81% and prior efavirenz in 19%) with an average plasma HIV-1 RNA level of 16,000 copies/mL and a CD4+ cell count of 464/ μ L, TMC 125 900 mg twice daily reduced mean plasma HIV-1 RNA level by nearly 1 \log_{10} from the baseline value

(Gazzard et al, 9th CROI, 2002). Further studies are in progress. The blunted antiretroviral response in NNRTI-experienced subjects compared with NNRTI-naive subjects in these pilot studies suggests that some degree of resistance is conferred by NNRTI-associated mutations. This concern supports the early discontinuation of currently available NNRTI-based regimens after confirmed virologic failure, in order to avoid the accumulation of additional NNRTI-associated mutations that may compromise the activity of investigational NNRTIs, including TMC 125.

HIV Protease Inhibitors

Atazanavir

Atazanavir is an azapeptide PI in development. It exhibits a 90% inhibitory concentration (IC₉₀) for HIV in vitro of 60 to 80 nM (adjusted for protein binding).

Pharmacokinetic data support once-daily dosing, which would make the compound unique among currently approved PIs without ritonavir boosting; the proposed dose is two 200-mg pills with food once daily. The drug is metabolized by the CYP 3A4 hepatic enzyme system. Adverse effects include an indirect hyperbilirubinemia, similar to that observed with indinavir. Minimal or no lipid changes have been observed with administration of the drug in clinical studies.

Atazanavir is in phase 3 testing. It is also currently available through an expanded-access program for patients with CD4+ cell count less than 300/ μ L and plasma HIV-1 RNA level greater than 5000 copies/mL, or with any viral load if triglyceride or total cholesterol levels are greater than 750 mg/dL and the patient is not responding to lipid-lowering therapy. Information about the expanded access program is available by calling 1-877-726-7327.

In a phase 3 study in 467 treatment-naive patients with a plasma HIV-1 RNA level greater than 2000 copies/mL and a CD4+ cell count greater than 75/ μ L, stavudine/lamivudine was given with

atazanavir at a daily dose of 400 mg (n=181) or 600 mg (n=195) or nelfinavir 1250 mg twice daily (n=91; Sanne et al, 41st ICAAC, 2001). In an intent-to-treat analysis, approximately 65% had a plasma HIV-1 RNA level less than 400 copies/mL and approximately 40% of patients in each arm had a level less than 50 copies/mL at 48 weeks. Overall, virologic response rates in both arms of this study were somewhat lower than other phase 3 studies of PIs, including nelfinavir, for unclear reasons. There was a significant difference in the change in total cholesterol levels between the groups, with an approximate 25% increase from baseline observed in the nelfinavir group compared with a 5% increase in the atazanavir groups by week 48.

In another study in patients failing current therapy, 85% of whom had received prior PI treatment, 85 patients with a plasma HIV-1 RNA level of 2000 to 100,000 copies/mL and a CD4+ cell count greater than 100/ μ L received atazanavir 400 mg or 600 mg plus saquinavir 1200 mg once daily, or ritonavir 400 mg plus saquinavir 400 mg twice daily. Of note, saquinavir and atazanavir

exhibit a pharmacokinetic interaction that increases blood levels of both drugs. Analysis of observed data in a total of 51 patients at 48 weeks showed that all 3 treatment regimens were associated with median reductions in viral load of approximately 1.2 to 1.6 log₁₀ (Haas et al, 9th CROI, 2002).

Recent data suggest atazanavir may have a unique initial resistance profile among the PIs. In a substudy of 76 subjects from phase 3 studies treated with atazanavir-based regimens who experienced virologic failure, 17 subjects displayed reduced susceptibility (5- to 141-fold) to atazanavir, and resistance patterns depended on prior PI experience (Colonno et al, *Antivir Ther*, 2002). Of 9 treatment-naive subjects who experienced virologic failure on atazanavir, 8 had a unique substitution at protease I50L, and this substitution actually appeared to increase susceptibility in vitro to many of the currently available PIs. In contrast, the 8 PI-experienced patients lacked the I50L substitution and demonstrated a loss of susceptibility to both atazanavir and the other PIs. Further resistance studies are in progress.

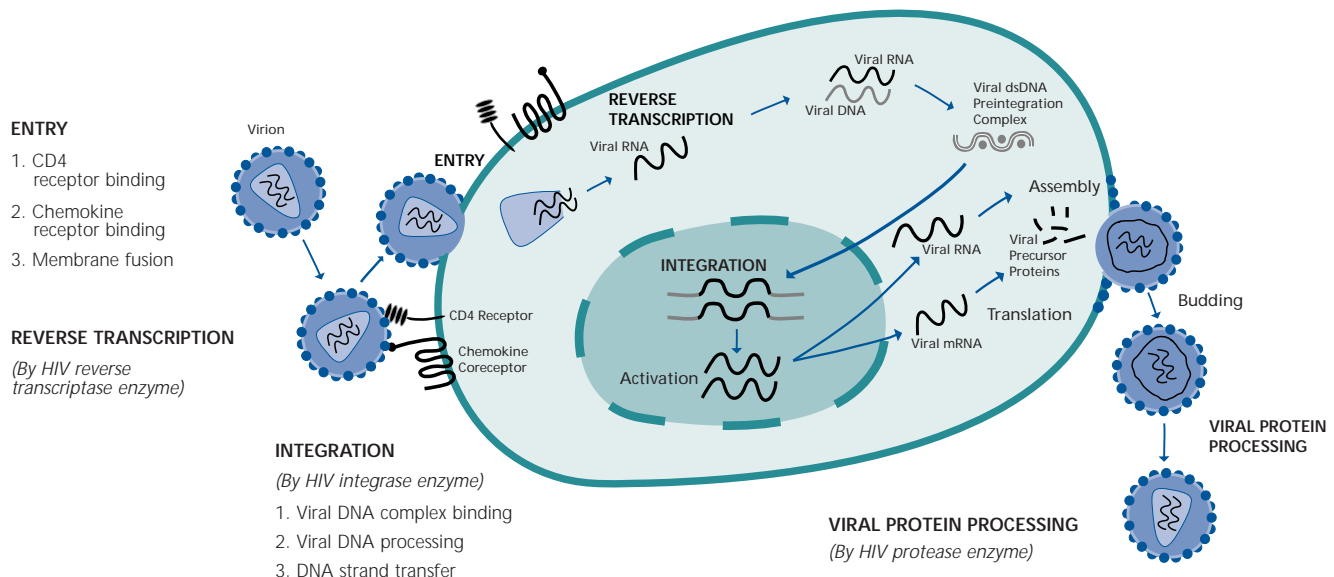


Figure 1. The life cycle of HIV-1. At left, the virion is shown attaching to the CD4 receptor and chemokine coreceptor and subsequently entering the host CD4 cell. Inside the cell, transcription of HIV RNA to HIV DNA is catalyzed by the HIV reverse transcriptase enzyme. The HIV DNA then forms a double-stranded DNA (dsDNA) complex, enters the host cell nucleus and integrates with the host genetic material via the HIV integrase enzyme. Upon activation, the viral DNA is transcribed into viral messenger RNA (mRNA) that in turn is translated into viral precursor proteins. The new HIV RNA and viral precursor proteins are assembled and the virus buds and is released from the cell surface. After budding, viral precursor proteins undergo processing by the HIV protease enzyme and form a mature, infectious viral particle.

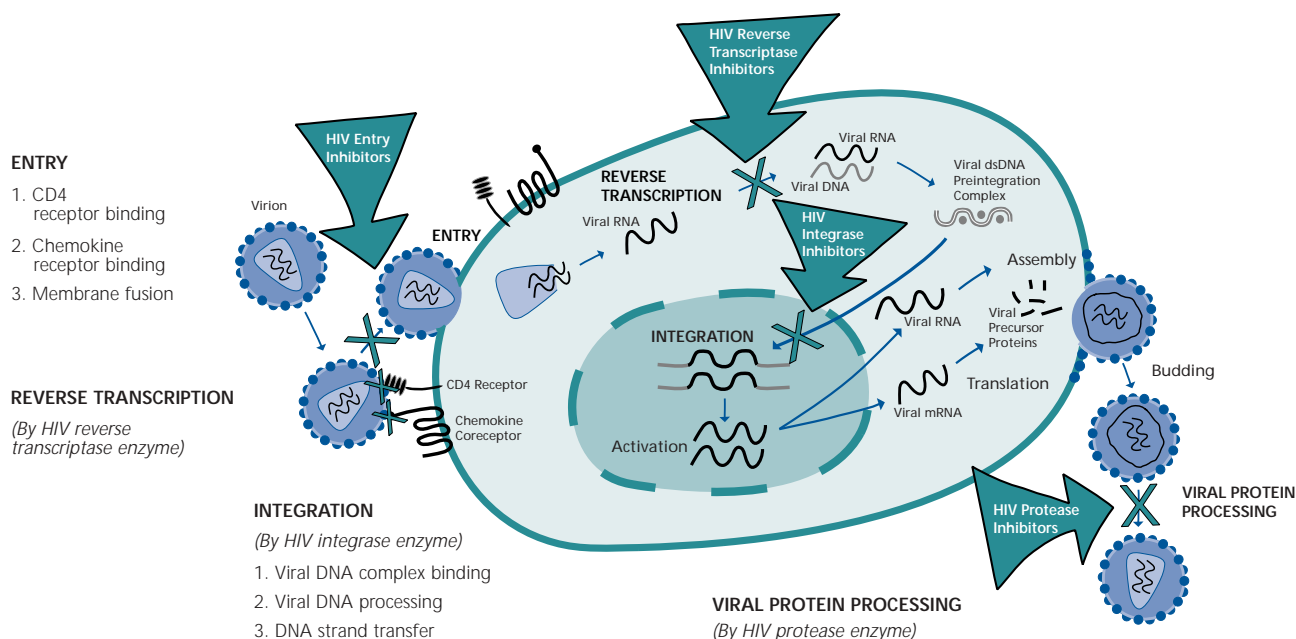


Figure 2. Stages of the HIV-1 life cycle targeted by currently approved and new investigational classes of anti-HIV drugs. The dsDNA indicates double-stranded DNA; mRNA, messenger RNA.

Tipranavir

Tipranavir is a nonpeptidic investigational PI with a 90% effective concentration (EC_{90}) of 0.5 to 1.0 μ M for HIV in vitro. It is active in vitro against a large majority of clinical HIV isolates resistant to indinavir, zidovudine, zalcitabine, and zalcitabine. Coadministration with ritonavir increases trough tipranavir concentrations by 7- to 40-fold, allowing the compound to be dosed twice daily, and absorption is increased if the drug is taken with a high-fat meal. The compound has been developed with a new self-emulsifying drug delivery system (SEDDS). It is metabolized via the CYP 3A4 hepatic enzyme system. Tipranavir currently is in phase 1/2 testing.

Tipranavir was evaluated in a pilot study in patients in whom treatment with 1 PI had failed. Enrollment criteria were baseline plasma HIV-1 RNA level greater than 1000 copies/mL and any CD4+ cell count. Sixty-two patients received one of 2 regimens: 2 new nRTIs with either tipranavir 500 mg or 1250 mg twice daily plus zidovudine 100 mg twice daily, or zalcitabine (soft gel capsule) 400 mg plus zidovudine 400 mg twice daily. Intent-to-treat analysis showed that approximately 60% of patients receiving tipranavir regimens and approximately

50% of those receiving the zalcitabine regimen had a greater than 1- \log_{10} decrease in plasma HIV-1 RNA level at 16 weeks (Slater et al, 41st ICAAC, 2001). The effectiveness of tipranavir in PI-experienced patients requires further evaluation.

TMC 114

TMC 114 demonstrates in vitro activity against a majority of clinical HIV isolates with resistance to zalcitabine, zalcitabine, zalcitabine, and amprenavir. The first study of this investigational PI in healthy volunteers has been reported and studies in HIV-infected patients are under way.

HIV Entry Inhibitors

HIV enters target (CD4) cells by initially binding to the CD4 receptor (Figure 1). Interaction with the CD4 receptor induces a conformational change in the HIV gp120 that allows binding to a second receptor, the chemokine coreceptor (CCR5 and/or CXCR4). This induces another conformational change in the HIV gp41 protein, bringing the viral and cell surfaces into contact. Fusion of the viral and cell membranes completes viral entry. Candidate drugs for blocking HIV entry thus include CD4 attachment

inhibitors, chemokine coreceptor inhibitors, and fusion inhibitors (Figure 2).

SCH-C

SCH-C (SC-351125) is a small-molecule binder of the CCR5 chemokine coreceptor with in vitro activity against HIV strains using the CCR5 coreceptor (IC_{90} ~20 nM) and against hybrid strains using both the CXCR4 and CCR5 coreceptors. Although there is a theoretical concern that a CCR5 inhibitor could promote a switch to the CXCR4 coreceptor (present with more virulent X4 viral strains), in mouse studies, emergence of resistance to SCH-C did not result in coreceptor switch (Moore, 1st IAS Conf on HIV Pathog and Treat, 2001). SCH-C is orally bioavailable, and pharmacokinetic data indicate a half-life of 4 to 6 hours, supporting twice-daily dosing. The mechanisms of metabolism of the drug have not been fully defined, but they do not appear to involve cytochrome P450 hepatic metabolism. In a phase 1 dose-escalation study in healthy volunteers given single doses of SCH-C, a prolongation (>50 msec) of the QTc interval was observed in 1 subject at the highest dose tested, 600 mg. In a phase 1 study in 28 HIV-infected patients, treatment with SCH-C 25 mg

twice daily produced a 0.5- to 0.7- \log_{10} decrease and treatment with 50 mg twice daily produced a 1.0- \log_{10} decrease from baseline plasma HIV-1 RNA levels at 10 days (Baroudy, 14th Int AIDS Conf, 2002). With proof of concept that a chemokine receptor inhibitor demonstrates antiretroviral activity in clinical studies, further dose-escalation studies are anticipated. A related compound, SCH-D, is also under investigation.

Enfuvirtide

Enfuvirtide (T-20) is a peptide fusion inhibitor that is given subcutaneously at a proposed dose of 90 mg twice daily. Adverse effects are primarily injection site reactions. Resistance mutations to enfuvirtide have been observed in vitro and in vivo and appear to involve mutations in gp41.

In a phase 1 study (Kilby et al, *Nat Med*, 1998) in which 16 patients received 4 different intravenous doses for 14 days, a 2- \log_{10} decrease in plasma HIV-1 RNA level was observed at the highest dose. Activity of the subcutaneous formulation has been demonstrated in both phase 2 and 3 studies, and the drug is now available under an expanded-access program.

In 2 recently presented phase 3 studies, the use of enfuvirtide led to improved virologic suppression when added to an optimized antiretroviral regimen in treatment-experienced subjects (Henry et al, 14th Int AIDS Conf, 2002; Clotet et al, 14th Int AIDS Conf, 2002). In the TORO (T-20 vs optimized regimen only)-1 study, HIV-infected patients with at least 6 months of prior treatment experience with all 3 classes of available antiretroviral drugs and an HIV-1 RNA level of greater than 5000 copies/mL underwent both genotypic and phenotypic resistance testing and selected a new antiretroviral regimen. They were then randomized 2:1 to add enfuvirtide to the regimen (90 mg subcutaneously twice daily) or not. A total of 491 subjects were randomized with a baseline HIV-1 RNA level of 159,000 copies/mL and CD4+ count of 80 cells/ μ L. The subjects had taken an average of 12 prior antiretroviral drugs and 80% had demonstrated 5 or more primary resistance mutations to all 3 antiretroviral drug classes. At 24 weeks, an

intent-to-treat, last-observation-carried-forward analysis demonstrated a highly significant mean change from baseline plasma HIV-1 RNA of $-1.7 \log_{10}$ copies/mL (enfuvirtide plus optimized regimen group) versus $-0.8 \log_{10}$ copies/mL (optimized regimen only group). The TORO-2 study of 504 patients demonstrated similar results. In both studies, the most common adverse experience was injection site reactions, but drug discontinuation for that reason was uncommon.

T-1249

T-1249 is structurally similar to enfuvirtide and was constructed by combining gp41 sequences from HIV-1, HIV-2, and simian immunodeficiency virus. The drug is also administered subcutaneously. T-1249 is 2 to 100 times more active against HIV in vitro than enfuvirtide and retains significant activity against enfuvirtide-resistant strains (Greenberg et al, *Antivir Ther*, 2002). Because enfuvirtide-associated resistance substitutions may confer some degree of cross-resistance to T-1249, consideration should be given to early discontinuation of enfuvirtide-containing regimens after virologic failure develops, to avoid the accumulation of additional substitutions. The investigational drug is currently in phase 1/2 evaluation.

In a phase 1/2 dose-escalation study, the area under the drug concentration-time curve and the minimum blood concentration were dose-proportional with once-daily dosing for 14 days. After a 4-week washout period, 63 patients received T-1249 6.25 mg, 12.5 mg, or 25 mg once or twice daily for 14 days. Sixty-two patients were antiretroviral-experienced, with prior exposure to an average of 10 drugs. At day 14, reductions in plasma HIV-1 RNA level were approximately 1.3 \log_{10} in the 25 mg twice-daily group, and 0.7 \log_{10} in the 25 mg once-daily group (Eron et al, 8th CROI, 2001). Data from additional studies of the drug should be available in the near future.

HIV Integrase Inhibitors

In addition to the HIV reverse transcriptase and protease enzymes, the third viral-specific enzyme is HIV integrase.

This enzyme promotes 3 specific steps of HIV integration: (1) binding to the viral DNA complex; (2) processing of viral DNA; and (3) DNA strand transfer whereby viral DNA is inserted into host cell DNA (Figure 1). As a unique viral-specific enzyme, it is an attractive target for antiretroviral drug development (Figure 2).

S-1360

S-1360, a small-molecule HIV integrase inhibitor, is the first of the HIV integrase inhibitors to reach clinical testing. S-1360 has an EC_{50} value of 0.025 to 0.074 μ g/mL for HIV in vitro before protein binding. Pharmacokinetic data suggest that the drug can be dosed orally 2 or 3 times daily; it is greater than 99% protein bound and is not metabolized via the CYP 3A4 system. Emergence of resistance in vitro has been associated with novel mutations in the HIV integrase active site. Administration in healthy volunteers has produced few adverse effects. S-1360 is currently being evaluated in phase 1 studies in treatment-experienced HIV-infected patients with CD4+ cell counts greater than 100/ μ L (Yoshinaga et al, 9th CROI, 2002).

L-870812 and L-870810

In vitro, diketoacids demonstrated potent anti-HIV integrase activity as strand transfer inhibitors, but these negatively charged candidates were not clinical candidates. Modification of these compounds led to the identification of a series of compounds with improved antiretroviral potency and pharmacokinetic characteristics, including good oral bioavailability. In monkeys, L-870812 was administered orally as a single agent and demonstrated virologic suppression of 1 to 3 \log_{10} copies/mL and preserved CD4+ cell counts for a 75-day period (Hazuda et al, *Antivir Ther*, 2002). A related compound, L-870810, currently is under investigation in healthy volunteers, and studies in HIV-infected subjects are anticipated.

Conclusion

New antiretroviral drugs are needed to improve convenience, tolerability, safety, and antiviral activity of antiretroviral

therapy. Promising agents are in development in existing classes (ie, reverse transcriptase and protease inhibitors) and in new classes (eg, HIV entry and HIV integrase inhibitors). Additional steps in the viral life cycle, including viral uncoating and viral assembly, and other enzymes, such as RNAase H, can and should be targeted in future drug development. Additional approaches using immune therapies such as interleukin-2 and therapeutic HIV vaccines may complement the use of current and future antiretroviral agents. Further basic and clinical research aimed at identifying and developing promising antiretroviral agents is needed.

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