NEW ANTIRETROVIRAL AGENTS FOR TREATMENT-EXPERIENCED PATIENTS*

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ABSTRACT

Antiretroviral treatment regimens currently available for the treatment of human immunodeficiency virus (HIV) infection are complex and inconvenient for patients and are associated with high rates of toxicity, drug resistance, and patient nonadherence to therapy. Several new antiretroviral treatments are currently in clinical development, and many of these medications have been shown to suppress HIV replication with high potency. New agents that are in phase II or phase III clinical trials include nucleoside reverse transcriptase inhibitors (eg, D-D4FC); nonnucleoside reverse transcriptase inhibitors (eg, tipranavir, TMC-114); HIV entry inhibitors (eg, TNX-355; UK-427,857; AMD-070); and maturation inhibitors (eg, PA-457). All of these agents have been shown to produce significant HIV viral suppression, including the suppression of viral strains that are resistant to other antiretroviral drugs. Tipranavir, a new agent that is close to receiving US Food and Drug Administration approval, may enter clinical practice within the next year; several other agents are currently in phase II clinical trials. (Adv Stud Med. 2005;5(2A):S117-S122)

The US Food and Drug Administration has currently approved 20 antiretroviral drugs, 4 improved drug formulations, and 5 fixed-dose combinations for the treatment of human immunodeficiency virus (HIV) infection. Despite the large number of available agents, significant challenges and unmet needs remain. The available treatment regimens often are complex and inconvenient for patients, resulting in treatment nonadherence. The available regimens also may be associated with considerable toxicity, variable penetration of virus reservoirs (eg, the central nervous system, retina, and genital tract), and the emergence of drug resistance and cross-resistance. To overcome these limitations, several new antiretroviral agents are currently in development, including new members of well-known therapeutic classes (eg, HIV reverse transcriptase inhibitors and protease inhibitors [PIs]), in addition to medication classes with novel mechanisms of action (eg, inhibitors of HIV entry, HIV maturation/gag processing, and HIV integrase). This paper reviews recent clinical studies that have examined the pharmacokinetics and antiretroviral activity of several agents currently in development, paying particular attention to new compounds designed to act against treatment-resistant HIV strains.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR: D-D4FC

D-D4FC is an investigational cytosine reverse transcriptase inhibitor with in vitro activity against wild-type HIV and against viral strains that are resistant to zidovudine, lamivudine, and tenofovir disoproxil fumarate. D-D4FC has a long half-life (approximately 17 hours) and has been evaluated for once-daily dosing. In a phase I clinical trial, 30 treatment-naive patients were randomly assigned to receive once-daily treatment with a placebo or 1 of 3 D-D4FC doses (50

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mg, 100 mg, or 200 mg). On the 10th day of treatment, patients in each of the D-D4FC dose groups exhibited approximately a 1.7-log mean reduction in HIV RNA, which returned to baseline levels when treatment was discontinued. No change in viral load was noted in the patients in the placebo group. In addition, these investigators examined the effects of this compound in 8 patients who had previously been treated with nucleoside reverse transcriptase inhibitors and who had a nucleoside-resistant virus. Patients treated with a D-D4FC dose of 200 mg once daily showed an average 0.8-log reduction in HIV viral load on the 10th day of treatment. Although based on a small number of patients, these results suggest that D-D4FC is effective against wild-type and nucleoside-resistant virus, although the drug may have less activity against nucleoside-resistant HIV. Larger clinical trials with D-D4FC are in progress.

**NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**

Each of the currently available nonnucleoside reverse transcriptase inhibitors (NNRTIs) produces drug-resistant viral strains that are completely cross-resistant to the other NNRTIs. Therefore, the most significant unmet need in this drug class is an NNRTI that is effective against NNRTI-resistant strains. One candidate compound is TMC-125, an investigational NNRTI. All of the currently available NNRTIs are rigid molecules that bind reverse transcriptase at the same site. For this reason, a viral mutation at the binding site confers resistance to all of the available NNRTIs. In contrast, TMC-125 is thought to have a more flexible molecular structure and to bind to HIV at a site that is distinct from the binding site used by available NNRTIs. Similar to other NNRTIs, TMC-125 is metabolized by the CYP3A4 enzyme system and by glucuronidation—making it distinctive from the other agents. Plasma levels of TMC-125 are reduced by ritonavir, and there may be drug-to-drug interactions with other PIs, which could complicate the use of TMC-125 in combination therapy regimens.

The effect of TMC-125 was examined in more than 1000 clinical isolates from patients who developed resistance to nevirapine, delavirdine, or efavirenz. Although most of the isolates were resistant to all 3 of the currently approved NNRTIs, approximately 80% were susceptible to TMC-125. A second study compared the effects of efavirenz and TMC-125 on several recombinant HIV strains with specific single, double, or triple mutations. Most of these mutations conferred high levels of resistance to efavirenz but not to TMC-125. In a pilot study comparing the anti-HIV effect of TMC-125 versus placebo in treatment-naive patients, 7 days of monotherapy with TMC-125 \((n = 12)\) produced a median 2-log decrease in HIV RNA from baseline, as compared with no change among patients who received a placebo \((n = 7; P < .001; \text{Figure})\). In a second pilot study of 16 patients with prior NNRTI experience (19% with efavirenz; 81% with nevirapine), TMC-125 produced approximately a 1-log mean decrease in viral load at 7 days. Phase II studies of TMC-125 are in progress.

**PROTEASE INHIBITORS**

Tipranavir, an investigational PI that is currently being evaluated in phase III clinical trials, is the new antiretroviral agent farthest along in development. In contrast with other PIs, which are structurally similar to peptide molecules, tipranavir has a distinctive nonpeptide molecular structure. In vitro studies suggest tipranavir is potent, with a 50% effective concentration of approximately 0.5 to 1.0 µM against wild-type virus. Tipranavir is available in a soft gel formulation at a dose of 250 mg per capsule.

![Figure. TMC-125 (versus Placebo) x 7 Days in Naive Subjects](image-url)

**Administration of TMC-125 produced approximately a 2-log reduction in HIV viral load during 7 days of treatment, compared with a 0.05-log reduction from baseline with placebo \((P < .001)\).**

**VL = viral load.**

The trough plasma concentration is increased from 7-fold to 40-fold when tipranavir is administered with ritonavir, permitting twice-daily dosing; the current proposed dosage is tipranavir 500 mg with ritonavir 200 mg twice daily. As with other PIs, tipranavir is metabolized by the CYP3A4 enzyme system. In general, HIV mutations at positions 33, 82, 84, and 90 are thought to confer broad resistance against PIs and are sometimes referred to as universal PI-associated mutations. Preliminary clinical evidence (described later in this article) suggests that tipranavir may demonstrate activity against some viral strains with these resistance mutations.

Tipranavir has been evaluated in a phase II clinical trial of patients who had previously received 3-class treatment, with evidence of at least 1 PI-associated mutation (but only 1 of the following protease substitutions: 82L/T, 84V, or 90M) at baseline. Before treatment, the patients had a mean viral load of 34,000 copies/mL and a mean CD4 cell count of 153 cells/µL. The patients’ existing PI was replaced by 1 of 3 doses of tipranavir in combination with ritonavir: tipranavir/ritonavir 500 mg/200 mg (n = 73); 500 mg/200 mg (n = 72); or 750 mg/200 mg (n = 71). All 3 regimens produced significant decreases of approximately 1 log copies/mL HIV RNA after the first 14 days. At this point, background treatment was optimized on the basis of resistance testing, and durable HIV RNA reductions continued over 8 weeks. Toxicities occurred more at the highest dose tested. A second study examined the effect of 3-PI regimens incorporating tipranavir in patients who had failed to respond to 3 medication classes (including a 2-PI regimen). Treatment failure was defined as a baseline viral load greater than 1000 copies/mL. Importantly, the patients had at least 3 of the important PI mutations (at positions 33, 82, 84, or 90). A total of 292 patients were enrolled in the study, with documented 40-fold to 350-fold phenotypic resistance to the other PIs at baseline. At the beginning of the study, the patients’ current PIs were substituted with 1 of 4 treatments (ie, tipranavir, amprenavir, saquinavir, or lopinavir), each of which was administered in combination with ritonavir. During the first 2 weeks of treatment, the tipranavir treatment resulted in a 1-log decrease in HIV RNA level, whereas the other treatments produced only approximately 0.2-log to 0.4-log decreases in HIV RNA levels. Tipranavir was then added to each of the other 3 PI combinations, resulting in approximately 1.2-log decreases in viral load in all 4 groups. Background treatment was not optimized in this study, and viral load levels began to increase again after 8 weeks of treatment. Adding tipranavir to the other PI/ritonavir combinations reduced the plasma concentrations of amprenavir, saquinavir, or lopinavir by approximately 50% to 70%. Phase III studies of tipranavir are fully enrolled.

A second new PI (TMC-114) is at an earlier stage of clinical development, but in vitro studies have demonstrated the high potency of TMC-114 activity against wild-type and PI-resistant viral strains. TMC-114 has a half-life of approximately 10 hours, is metabolized by the CYP3A4 enzyme system, and has a plasma concentration that is significantly increased by coadministration of ritonavir. In an in vitro study of more than 5000 clinical isolates containing 3 or more primary PI mutations, more than 50% of the isolates remained susceptible to TMC-114, whereas other PIs (indinavir, nelfinavir, saquinavir, amprenavir, lopinavir, atazanavir) retained activity against 20% or fewer of the PI-resistant isolates. In a study of 50 patients who had previously been treated with 2 to 4 PIs and were failing their current regimen, treatment with TMC-114 over 14 days at doses of 300 mg twice daily, 600 mg daily, or 900 mg daily, in combination with ritonavir, produced 1.3-log to 1.4-log decreases in HIV viral load from baseline. No decrease in viral load was noted among patients who received a placebo. In a follow-up analysis of 38 of these patients, the effects of TMC-114 were examined in different patient subgroups, including those who had more than one primary PI mutation, who had phenotypic resistance to all approved PIs, or who had greater than a 10-fold resistance to lopinavir/ritonavir at baseline. In each of these patient subgroups, virologic response was similar to that observed in the overall study population.

**New Agents with Novel Mechanisms of Action**

Entry of HIV into the CD4 lymphocyte is the first step in viral replication. HIV enters the cell in a 3-step process. HIV first binds to the CD4 receptor, which induces a conformational change in the HIV external membrane protein, GP120. This conformational change permits binding to a second receptor or coreceptor, known as the chemokine receptor. The chemokine receptors that facilitate HIV entry are CCR5 or CXCR4. CCR5-tropic virus (formerly called M-tropic virus or nonsyncytium-inducing virus) is more common throughout the entire course of HIV infection, whereas the CXCR4-tropic virus (formerly called T-tropic virus...
or syncytium-inducing virus) occurs in advanced HIV disease and is associated with more rapid progression of HIV disease. A newer assay, the cellular tropism assay, can determine the viral tropism of a given patient's viral strain: CCR5-tropic, CXCR4-tropic, or dual-tropic (for CCR5 and CXCR4). HIV binding to the chemokine receptor induces a second conformational change in the glycoprotein (gp) 120 molecule, allowing the gp41 protein of HIV to penetrate the cell membrane, fold in on itself, and draw HIV into contact with the cell membrane where the viral and cellular membranes fuse and the virus enters the cell. Each of these steps is a potential target where HIV entry may be blocked. New classes of agents have been developed to interfere with HIV entry at each of these steps, including the CD4 attachment inhibitors, chemokine receptor inhibitors (CCR5 and CXCR4 inhibitors), and fusion inhibitors. One fusion inhibitor, enfuvirtide, is currently approved by the US Food and Drug Administration for use in treatment-experienced patients.

TNX-355 is a humanized anti-CD4 monoclonal antibody that is administered parenterally once or twice weekly. In a phase IA single-dose study involving 30 previously treated patients, TNX-355 produced a dose-related suppression of HIV replication, with a 1.1-log reduction in HIV RNA at the highest dose tested. A phase IB multiple-dose study involving 22 patients examined 3 dosing regimens: 10 mg/kg once weekly; 10 mg/kg loading dose, followed by 6 mg/kg every 2 weeks; or 25 mg/kg every 2 weeks for a 9-week period. Overall, treatment produced a 1-log decrease in viral load levels at the end of 2 weeks, although the decrease was followed by a return to baseline after 9 weeks. A larger phase II clinical trial is in progress.

UK-427,857 (an investigational oral CCR5 chemokine receptor inhibitor) was evaluated in a study of 80 asymptomatic patients who were naive to treatment or off treatment for 8 weeks. The patients were required to have a viral load greater than 5000 copies/mL and a CD4 count less than 250 cells/µL, with evidence of CCR5-tropic virus using the viral tropism assay. Patients were randomly assigned to receive a placebo or to receive UK-427,857 doses of 25 mg, 100 mg, or 300 mg every day or 50 mg, 100 mg, 150 mg, or 300 mg twice daily. The 150-mg dose was evaluated with and without food. Patients were treated for 10 days, with an additional 30 days of follow-up. During the study, 2 of the patients showed tropism changes (CCR5-tropic to dual-tropic), whereas 61 of 63 patients remained with CCR5-tropic virus. One patient reverted to CCR5-tropic virus after stopping the CCR5 inhibitor; the other patient continued to have dual-tropic virus for a total of 6 months, although without evidence of clinical progression. Total daily doses of 200 mg or less per day resulted in approximately 1.3- to 1.5-log decreases in HIV RNA levels. Drug levels were reduced by approximately 50% when administered with food, although the antiviral activity was not affected. SCH 417690 (SCH D), a second CCR5 inhibitor, demonstrated similar suppression of HIV RNA levels in a phase I/II study presented in 2003. Treatment with SCH D at a dose of 10 mg twice daily produced a mean 1-log decrease in viral load over 14 days; doses of 25 or 50 mg twice daily produced approximately 1.5-log decreases in HIV RNA. The combination of SCH D and ritonavir is being evaluated in previously treated patients in larger studies, including the AIDS Clinical Trials Group (ACTG) study A5211.

AMD-070 is a CXCR4 receptor inhibitor that is active in vitro, with a reported 50% inhibitory concentration of 6.6 nM. In vitro studies report that AMD-070 acts synergistically with AMD-887, an investigational CCR5 inhibitor, suggesting that anti-HIV activity may be increased by combining inhibition of both chemokine receptors, although this has not been studied clinically. Initial pharmacokinetic studies found that single doses of AMD-070 produced sustained drug levels above the 90% effective concentration for wild-type HIV for over 12 hours.

The final strategy currently being evaluated in clinical trials is maturation (or gag processing) inhibition. PA-457, an inhibitor of gag processing, prevents the conversion of capsid precursor proteins to capsid protein (p24), which results in the release of a noninfectious virus. PA-457 has been shown to produce long-acting in vitro activity against wild-type and drug-resistant virus strains. The incubation of CD4 cells with PA-457 results in the development of poorly formed, noninfectious core particles. The first clinical trial of PA-457 will begin enrolling patients soon.

CONCLUSIONS

Several new agents are being developed to treat HIV infection. Many of these agents may be more effective for the treatment of drug-resistant viral strains than the currently available drugs. Tipranavir, the agent farthest along in development, is completing
DISCUSSION

Dr Masur: Many of these drugs, such as TMC-125, are being assessed as monotherapy in early trials. Is there any evidence that it’s unsafe for patients to participate in those trials?

Dr Gulick: The short answer is yes, there is concern regarding the development of resistance using monotherapy. It’s probably less of an issue with the candidate nucleosides and protease inhibitors because resistance develops more slowly; that’s why the optimized background step is included. However, recent data reporting that patients can become resistant to non-nucleosides with as little as a single dose raise the question of participation in early nonnucleoside studies. There is really no effective method for testing these drugs if resistance is expected to develop quickly. Thus, there is a challenge to the development of that class.

Dr Bartlett: It’s impressive that a 1- or 1.5-log drop occurs in a 2-week time frame with these drugs. The observation has been reported a long time, but it is not used clinically. The drug is administered and then 3 months later a viral load occurs. However, the good news is that if it’s going to work, the results come quickly.

Dr Gulick: There is a body of scientific literature to support that early changes are indicative of long-term responses. Therefore, why isn’t this used clinically? Of course, some physicians do prescribe monotherapy and are, perhaps, reassured by the overall response rates, but then the practical considerations are a hindrance. Even if there is a good 4- or 8-week response, adherence or toxicity can often impact longer-term responses.

Dr Masur: What if there is a slow response at 4 or 8 or 12 weeks? If a patient has a reduction but doesn’t meet those milestones, should therapy be intensified? Or should therapy be continued with the anticipation that a substantial fraction of patients will still have a sustained response? At what point should therapy be discontinued?

Dr Hirsch: It depends on the types of drugs, and those are the situations in which NNRTI resistance or lamivudine or emtricitabine resistance are likely to occur. With lopinavir/ritonavir, treatment may be continued a bit longer. And certainly, nevirapine pregnancy issues should be a concern during any therapy. Recent data have shown that even in 1-week or 2-week trials, a substantial proportion of women may develop nevirapine resistance mutations from a single dose.

Dr Gulick: With the drugs we have today, if you see a slow response you should not only check the viral load level but do a resistance test. There is the possibility that the patient was infected with a virus that already had drug resistance.

Dr Stone: What about ritonavir boosting? When patients present with high viral loads, some physicians are doubly boosting the lopinavir/ritonavir and using additional ritonavir. Is there a downside to making early decisions about the correct dosage of ritonavir in combination with tipranavir and the other PIs?

Dr Gulick: Data suggest the optimal ritonavir dose, which I think is most often chosen because of toxicity reasons. A phase II study investigated using lopinavir/ritonavir 100 mg twice daily or 200 mg twice daily and found similar or better activity at the higher dose. But 200 mg twice daily of ritonavir was not as well tolerated by patients. In terms of the indinavir/ritonavir dose, the ACTG study did a head-to-head comparison of 2 doses, as reported in ACTG 401. One group of patients received indinavir and ritonavir, both administered at 400 mg twice daily; the other group of patients received indinavir 1000 mg with ritonavir 200 mg twice daily. The investigators concluded that the optimal dose was somewhere in the middle.

Dr Bartlett: Therefore, it seems that tipranavir, which is probably the most interesting drug, would have to be used alone at least as a sole PI with ritonavir and is probably more effective based on the class mutations from the decrease you reported. Is that correct?

Dr Gulick: Yes. Those are phase II results from relatively smaller patient studies. It is difficult to explain that second study in which tipranavir had marked antiretroviral activity, but those are the data reported.

Dr Powderly: I disagree. Basically the effect was very consistent. Across all strata when tipranavir was added, approximately a 1-log reduction occurred at 14 days. These patients were highly resistant to virus; were randomly assigned to receive monotherapy; and, if they received the available drugs to which their virus was already resistant, had minimum response. When those patients received tipranavir, they had a 1-log reduction. There was nothing surprising about that result. The
challenge, not only from a study design perspective but in practice, is that the study response is not a durable response. Investigators have found in multiple studies over the past 10 years that adding a new agent to the regimen of a patient who already has resistant virus is likely to have merely a temporary effect.

It’s interesting when the data are studied in some detail. Although it was a phase II study, approximately 250 patients were enrolled, thus it was actually not a small study. Approximately 20% of the patients received concomitant T20 and were naive to T20, thus there was a small subset of patients across all of the arms of the study who received 2 new drugs—tipranavir and T20. Those patients seemed to have a more durable response. Also, the TORO (T-20 versus Optimized Regimen Only) studies reported the same data with T20. If these new drugs are used only in a true “salvage situation,” in which the patient has no other option, the drugs are of marginal benefit and have no durability. The same challenge arises in clinical practice and in drug development. The optimal benefit of these drugs can occur only when several of them are used at the same time.

Dr Gulick: But the in vitro data would suggest that if 3 or 4 of those important protease mutations were present, the antiviral activity of tipranavir was compromised.

Dr Powderly: But the phenotypic data from that study suggested that many of these viruses were still phenotypically quite susceptible to tipranavir. Thus, there may be a disconnection between the genotype and the phenotype the virus demonstrates with tipranavir.

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