Optimizing Therapy for Patients With Multidrug-Resistant HIV

Review and Updates to the 2005 ICAAC Satellite Symposium, Management of Treatment-Experienced Patients

A Free CME/CE/CEU Monograph

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There are many reasons why a treatment regimen fails, and such failure may be virologic, immunologic, and/or clinical. Approaches to handling these situations, and the goals of rescue therapy, vary and often depend on patients’ treatment histories. Strategies such as prospective resistance testing, pharmacokinetic enhancement with ritonavir, or the use of new antiretroviral agents may help optimize a regimen for patients who experience some form of treatment failure.

Factors that may result in antiretroviral failure include pre-existing resistance mutations, poor adherence, or inadequate potency or drug levels. Although changing the failing regimen may not always be necessary, the type and cause of treatment failure is important when determining whether a change of regimen is necessary and what subsequent regimens may be effective. Prospective resistance testing can identify drugs that will still be effective, and a number of strategies exist for identifying and improving regimens that fail because of suboptimal drug levels.

Pharmacokinetic enhancement has been a useful technique, and new strategies based on this are being investigated. Adding another protease inhibitor to an already boosted regimen may be useful in creating a single-class regimen but may be more effective as a rescue therapy for treatment-experienced patients. However, due to the variable interactions with the cytochrome P450 isoenzymes, double protease inhibitor-boosted regimens that contain two active protease inhibitors and ritonavir have complex pharmacokinetic profiles that can be effective but difficult to predict.

Resistance to the current classes of antiretrovirals has prompted the search for new agents in existing classes with different resistance patterns, along with new agents that target different parts of the virus life cycle. Recently approved agents for use in treatment-experienced patients include enfuvirtide, an entry inhibitor, and tipranavir, a nonpeptidic protease inhibitor. A number of new compounds for treatment-experienced patients are currently being tested in different phases of clinical trials. Some new agents, including those in development, that contain two active protease inhibitors and ritonavir have complex pharmacokinetic profiles that can be effective but difficult to predict.

For many patients, HIV has evolved into a manageable disease that requires long-term treatment. However, patients who have failed a number of different regimens are difficult to treat. Failure of a regimen usually results in the evolution of resistance mutations, and each new regimen usually brings with it a new set of mutations that can further limit potential treatment options. Therefore, it is important for clinicians to be aware of new agents and strategies for identifying and treating patients in order to maintain durable, long-term treatment of HIV.

**EDUCATIONAL OBJECTIVES**

Upon completion of this program, the participant should be able to:

- Define what is meant by virologic, immunologic, and clinical failure and the factors that influence treatment failure.
- Discuss different strategies for optimizing therapy in treatment-experienced patients.
- Explain the basis and benefits of pharmacokinetic enhancement and the complex drug-drug interactions between various protease inhibitors.
- Describe the clinical utility of current and new antiretrovirals in treatment-experienced patients.

**ACREDITATION AND CREDIT DESIGNATION**

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Use of Pharmacokinetic Enhancement in Antiretroviral Treatment-Experienced HIV Patients

Angela D.M. Kashuba, BScPhm, PharmD, DABCP

ABSTRACT

Protease inhibitors (PIs) are potent agents for controlling HIV infection. The physicochemical properties that make these drugs inherently effective for suppressing intracellular infection also predispose them to the effects of drug-metabolizing enzymes and transporters. This results in significant challenges to achieving adequate systemic exposure. A number of compounds have been investigated to inhibit metabolism and transport, thereby elevating drug concentrations. Low-dose ritonavir appears to be the most potent compound for inhibiting cytochrome P450 enzyme activity and P-glycoprotein activity. Its use as a pharmacoenhancer for most PIs has significantly improved the management of HIV. Most recently, dual PI therapy in combination with ritonavir has been explored as an option for treatment-experienced patients. This article will focus on the mechanisms of first-pass metabolism for PIs, how these activities can be overcome by ritonavir, and the theoretical benefits to dual-boosted PI therapy. Studies evaluating combinations of PIs will be reviewed to illustrate the complications of predicting these interactions and the need for formal pharmacokinetic studies. Additionally, the use of pharmacokinetic enhancement with new classes of antiretroviral agents will be discussed.

INTRODUCTION

Pharmacokinetic enhancement is the strategy of exploiting pharmacokinetics to optimize exposure to drug therapy. As currently applied to the management of HIV infection, it is used to increase exposure to protease inhibitors (PIs), all of which are associated with limited oral bioavailability. Typically, it involves enhancing or “boosting” exposure to a primary PI administered at a therapeutic dosage with a low, non-therapeutic dose of ritonavir (r), itself a PI. It is now well established that when boosted, some PIs exhibit greater virologic potency by increasing plasma trough concentrations, which provides an improved barrier against the development of antiretroviral drug resistance. In addition, boosted PI regimens extend the duration of adequate drug exposure, allowing less frequent dosing (in some cases to once a day, e.g., atazanavir/r, fosamprenavir/r and lopinavir/r). There is evidence that if necessary, this approach can also be useful for increasing exposure to fusion inhibitors that block viral entry via CCR5 chemokine co-receptors; currently, the lead CCR5 inhibitors in clinical trials are maraviroc (UK-427,857, Pfizer; phase III clinical trials) and vicriviroc (SCH 417690, Schering-Plough; phase II treatment-experienced HIV patients).

PI PHARMACOLOGY OVERVIEW

Oral bioavailability of PIs is generally low due to extensive first-pass metabolism by multidrug resistance transporters (particularly P-glycoprotein), and the cytochrome P450 system (CYP450) found in the intestine and the liver. Inter- and occasionally intra- individual expression of both P-glycoprotein and CYP3A4, the CYP450 isozyme primarily responsible for PI metabolism, is highly variable. Furthermore, most PIs are highly
protein bound in serum. As only free drug is pharmacologically active, inter-individual variations in the extent of protein binding may have significant effects on PI exposure as well as antiviral activity. These factors explain much of the observed inter-patient variability in the absorption, distribution, metabolism, and excretion of PIs and contribute to why patients may experience treatment failure.

First-pass Metabolism

P-glycoprotein

P-glycoprotein is an adenosine triphosphate-dependent drug efflux pump that protects cells from accumulating a wide range of toxic compounds. It is located on cell membranes and is expressed at high levels in a variety of tissues, including the gastrointestinal tract and liver. All currently available PIs are substrates for P-glycoprotein to a varying degree. Transport of PIs by P-glycoprotein may regulate their bioavailability by several mechanisms, including limiting their uptake in the small intestine and increasing their metabolism by intestinal CYP3A4 through repeated cycles of uptake and efflux. It is also worth noting that P-glycoprotein activity in other tissues such as the brain and testes may lead to protected sanctuaries of HIV replication as a result of limited drug accumulation at these sites. As well as being substrates for P-glycoprotein, PIs, particularly ritonavir, inhibit this transporter’s activity in various cells, including CD4 and CD8 cells and CD34+ progenitor cells. To complicate matters further, some PIs may also increase the activity of P-glycoprotein. For example, tipranavir has been reported to be a potent inducer of this transporter. Other drug transporters have also been implicated in the transport of PIs, although these interactions are not well defined.

CYP450

All PIs are metabolized by the CYP450 system in the intestine and liver, primarily by the CYP3A4 isoyme and to a lesser extent by CYP2D6, CYP2C9, and CYP2C19. The extensive first-pass metabolism by CYP450 reduces oral bioavailability of PIs to varying degrees. For example the bioavailability of saquinavir is <10%, while that of ritonavir and indinavir is >60%. As with P-glycoprotein, the situation is complicated by the fact that PIs are inhibitors and may also be inducers (lopinavir, ritonavir, amprenavir, tipranavir) of CYP3A4. Ritonavir is the most potent inhibitor, followed by amprenavir > indinavir > nelfinavir > saquinavir. The potent inhibition of CYP3A4 by low (non-therapeutic) doses of ritonavir has led to its utility in boosting exposure to the primary PI used at a therapeutic dose (PI/r).

Protein Binding

PIs generally bind to albumin and alpha-1-acid glycoprotein in blood plasma. Mean protein binding ranges from 60% for indinavir to ≥98% for lopinavir, nelfinavir, saquinavir and tipranavir. As an acute phase reactant, there can be significant intra- and inter-individual differences in the concentrations of alpha-1-acid glycoprotein. The clinical significance of these alterations on antiretroviral efficacy is unknown.

EXPOSURE AND RESPONSE

A narrow therapeutic window exists for many antiretroviral agents. Maintaining high plasma drug concentrations, and preventing these from dipping below the recommended minimal concentrations required for inhibition of viral replication during a dosing interval, increases the antiviral potency of PIs. On the other hand, all PIs are associated with adverse side effects and toxicities, and as such, increased exposure to these drugs may increase the incidence and/or severity of these. Thus, an “ideal” PI-based antiretroviral regimen would maintain high PI trough concentrations that provide adequate antiviral activity to protect against the development of drug resistance, and low peak concentrations that protect against toxicity. Although there are no strategies to markedly reduce peak concentrations, PI boosting has been widely adopted to maintain high PI trough concentrations that enhance antiviral efficacy. There are promising reports indicating that boosted PIs provide beneficial virological outcomes (described below). However, studies employing therapeutic drug monitoring have revealed that maintaining adequate plasma drug concentrations is not straightforward. The wide variability of plasma PI concentrations with specified doses of PIs and ritonavir may in some cases cause excessive
toxicity that leads to reduced adherence or, alternatively, insufficient plasma concentrations that lead to the development of resistance. For example, a study of patients receiving either indinavir or boosted indinavir found wide intra- and inter-patient variability in plasma indinavir concentrations (indinavir, mean = 3,260 ng/mL ± 3,385 ng/mL vs boosted indinavir, mean = 4,191 ng/mL ± 4,251 ng/mL, not significant).

**PHARMACOLOGIC ENHANCEMENT OF PIs**

**Pharmacokinetic Effects of Ritonavir on Other PIs**

Ritonavir is by far the most common compound used in clinical practice to boost the antiviral activity of PIs for the treatment of HIV infection. Its inhibitory effects on CYP450 and P-glycoprotein can increase the extent of absorption and slow the clearance of the primary PI, which raises plasma trough concentrations and may also raise peak concentrations (Figure 1). The boosting effects of ritonavir are specific to individual PIs, all of which may be boosted for clinical purposes except for nelfinavir, on which it has little effect. Furthermore, as both ritonavir and nelfinavir have been associated with diarrhea, with rates of 30-40% reported with the latter, combining these agents may further exaggerate this side effect. The pharmacokinetic effects of ritonavir boosting of individual PIs are summarized in Table 1.

**Clinical Experience With Boosted PIs**

There is accumulating clinical data indicating that boosted PI regimens are equivalent or more efficacious than single PI regimens in treatment-naive and -experienced patients.

**Comparisons of un-boosted versus boosted PIs**

*Indinavir/r.* Boosting indinavir with ritonavir simplifies therapy by allowing twice-daily dosing and removing the need for dietary restrictions. A comparison of indinavir/r 800 mg/100 mg bid versus indinavir 800 mg tid in combination with zidovudine/lamivudine in nucleoside-experienced HIV-infected patients demonstrated similar antiviral activity after 112 weeks of follow-up (percentage of patients with viral load <50 copies/mL, 64% vs 59%, \( P = 0.86 \)).

**Comparisons of a boosted PI with nelfinavir**

*Fosamprenavir/r.* Fosamprenavir is a prodrug of amprenavir that, when combined with ritonavir, offers a once-daily dosing option for the treatment of antiretroviral-naive HIV-infected patients.

![Figure 1. Pharmacological enhancement: “boosting” of protease inhibitors (Pis).](image-url)
A comparison of fosamprenavir/r 1400 mg/200 mg once daily versus nelfinavir 1250 mg bid in combination with abacavir/lamivudine in antiretroviral-naive HIV-infected patients demonstrated similar antiviral activity after 48 weeks of therapy (percentage of patients with viral load <50 copies/mL, 55% vs 53%).

Lopinavir/r. Lopinavir is co-formulated with ritonavir. This helps simplify dosing by reducing the pill burden of the individual agents. A comparison of lopinavir/r 400 mg/100 mg bid versus nelfinavir 750 mg tid in combination with stavudine/lamivudine in antiretroviral-naive HIV patients demonstrated superior antiviral activity of the lopinavir regimen after 48 weeks of follow-up (percentage of patients with viral load <50 copies/mL, 67% vs 52%, *P* < 0.001).

Comparisons of boosted PI regimens

**Atazanavir/r** versus **lopinavir/r**. Atazanavir is an azapeptidase PI that has the advantage of once-daily dosing. Boosted atazanavir has only been tested in clinical trials of treatment-experienced patients to date. A comparison of atazanavir/r 300 mg/100 mg once daily versus lopinavir/r 400 mg/100 mg bid in combination with tenofovir and one nucleoside reverse transcriptase inhibitor (NRTI) in HIV patients who had failed HAART regimens containing PIs demonstrated similar antiviral activity after 48 weeks of follow-up (decrease in HIV RNA from baseline, 1.58 vs 1.70 log_{10} copies/mL). (The study was not powered to detect similarity between efficacy of regimens to achieve viral load below the limit of detection.)

**Saquinavir/r** versus **indinavir/r** or **lopinavir/r**. Boosting saquinavir with ritonavir provides a significant increase in bioavailability (Table 1). The new 500-mg tablet formulation of saquinavir now offers a reduced pill burden.

A comparison of saquinavir/r 1000 mg/100 mg bid versus lopinavir/r 400 mg/100 mg bid in combination with two or more NRTIs/NNRTIs in antiretroviral-naive, PI-naive, or PI-experienced HIV patients demonstrated superior antiviral activity of the lopinavir/r regimen after 48 weeks of follow-up (percentage of patients with virological failure, 33% vs 18%, *P* = 0.002).

**Tipranavir/r**. Boosted tipranavir is indicated for combination therapy for the treatment of HIV-1–infected adults who have evidence of viral replication, are highly treatment-experienced, or have multiple–PI-resistant HIV-1 strains.

A comparison of tipranavir/r 500 mg/200 mg bid versus comparator PI (lopinavir, amprenavir,

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**Table 1.** Effects of ritonavir boosting on the pharmacokinetics of protease inhibitors (PIs).

<table>
<thead>
<tr>
<th>Primary PI</th>
<th>Dose (Primary PI/r)</th>
<th>Fold-change in primary PI (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Atazanavir&lt;sup&gt;22&lt;/sup&gt;</td>
<td>300 mg/100 mg qd</td>
<td>1.9-fold ↑</td>
</tr>
<tr>
<td>Fosamprenavir&lt;sup&gt;23&lt;/sup&gt;</td>
<td>1400 mg/200 mg qd</td>
<td>1.5-fold ↑</td>
</tr>
<tr>
<td></td>
<td>700 mg/100 mg bid</td>
<td>1.3-fold ↑</td>
</tr>
<tr>
<td>Indinavir&lt;sup&gt;27&lt;/sup&gt;</td>
<td>800 mg/100 mg bid</td>
<td>1.6-fold ↑</td>
</tr>
<tr>
<td></td>
<td>800 mg/200 mg bid</td>
<td>1.2-fold ↑</td>
</tr>
<tr>
<td>Lopinavir&lt;sup&gt;24&lt;/sup&gt;</td>
<td>400 mg/50 mg single dose</td>
<td>55-fold ↑</td>
</tr>
<tr>
<td>Saquinavir (hard-gel)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>1000 mg/100 mg bid</td>
<td>13.3-fold ↑</td>
</tr>
<tr>
<td>Tipranavir&lt;sup&gt;d&lt;/sup&gt;</td>
<td>500 mg/200 mg bid</td>
<td>4-fold ↑</td>
</tr>
</tbody>
</table>

C<sub>max</sub> = maximum drug concentration; C<sub>min</sub> = minimum drug concentration; AUC = area under the plasma concentration curve; qd = once daily.
saquinavir, or indinavir)/r in combination with an optimized background regimen in extensively pretreated HIV patients demonstrated superior antiviral activity of the tipranavir/r regimen after 24 weeks of follow-up in this patient population (percentage of patients with at least 1 log₁₀ HIV-1 RNA decrease, 40% vs 18%).

**Common dosing of boosted PIs in clinical practice**

Common dosing of ritonavir-enhanced PI combinations is shown in Table 2. Of note, hard-gel saquinavir (now available in tablet form) has improved gastrointestinal tolerance compared to the soft-gel formulation. Since ritonavir boosting of saquinavir produces similar plasma exposure to saquinavir for both formulations, the former may be preferred. Furthermore, the improved tolerability of the hard tablet formulation is facilitating investigations of higher doses of saquinavir (up to 2000 mg with 100 mg or 200 mg of ritonavir once daily).

**Double-boosted PIs**

Double-boosted PI therapy is the combination of a boosted PI combination with another PI administered at therapeutic doses. This strategy has become a new area of investigation for the treatment of HIV-infected patients who have extensive resistance. In these patients, one boosted PI may retain activity despite the evolution of HIV variants that are resistant to the other.

Theoretically, favorable ritonavir-boosted combinations may include the use of agents that show synergy, complementary resistance patterns, or those with mutually exclusive resistance profiles. For example:

- Saquinavir and lopinavir — synergistic inhibition of HIV replication has been demonstrated between these agents in vitro.
- Saquinavir and atazanavir — atazanavir has a unique I50L signature resistance mutation that produces increased susceptibility to indinavir, lopinavir, ritonavir, and saquinavir. Furthermore, atazanavir remains susceptible after selection of L90M, a primary mutation associated with resistance to saquinavir.
- Saquinavir and amprenavir — these PIs have distinct mutations associated with reduced susceptibility (amprenavir, V32I, M46I/L, I47V, I50V, I54L/M, and I84V; saquinavir G48V and L90M).
- Atazanavir and amprenavir — substitution of I50L or I50V produces mutually exclusive resistance to atazanavir and amprenavir, respectively, without cross-resistance.

However, no prospective comparative-outcome data regarding the efficacy of double-boosted PIs compared to single-boosted PIs are yet available. As multiple interactions with P-glycoprotein, CYP450 isoenzymes, and plasma-binding proteins influence PI pharmacokinetics, the net effect of combination regimens containing more than two PIs is very difficult to predict.

**Studies of pharmacokinetic interactions of double-boosted PIs**

The pharmacokinetic effects of adding an additional PI to a boosted regimen have been evaluated in a number of studies in healthy volunteers and HIV-infected patients. These studies show that although some combinations result in pharmacokinetic enhancement, others lead to significant reductions in drug exposure.

**Saquinavir/r plus atazanavir.** The combination of atazanavir 300 mg once daily with saquinavir/r 1600 mg/100 mg once daily was evaluated in HIV patients who had been receiving a stable antiretroviral regimen containing saquinavir/r and two NRTIs. Over 24 hours, the double-boosted regimen significantly increased saquinavir and ritonavir exposure (Table 3). Atazanavir concentration was not significantly affected.
**Table 3.** Effect of double-boosted regimen of saquinavir/r plus atazanavir on pharmacokinetics.33

<table>
<thead>
<tr>
<th>Trough concentrations</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>↑ 112%</td>
<td>↑ 60%</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↓ 27%*</td>
<td>↑ 41%</td>
</tr>
</tbody>
</table>

*Not significant.

**Lopinavir/r plus fosamprenavir.** The combination of fosamprenavir 700 mg bid and lopinavir/r 400 mg/100 mg bid compared with fosamprenavir/r 700 mg/100 mg bid was evaluated in healthy volunteers. The double-boosted regimen decreased amprenavir and lopinavir exposure (Table 4). Furthermore, similar decreases were observed in PI-experienced HIV patients (Table 5).

**Table 4.** Effect of double-boosted regimen of lopinavir/r plus fosamprenavir on pharmacokinetics in healthy volunteers.34

<table>
<thead>
<tr>
<th>Trough concentrations</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>↓ 78%</td>
<td>↓ 76%</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>↓ 49%</td>
<td>↓ 25%</td>
</tr>
</tbody>
</table>

**Table 5.** Effect of double-boosted regimen of lopinavir/r plus fosamprenavir on pharmacokinetics in PI-experienced patients.35

<table>
<thead>
<tr>
<th>Trough concentrations</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>↓ 64%*</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>↓ 48%*</td>
</tr>
</tbody>
</table>

*P < 0.0001; †P = 0.0001; ‡P = 0.0008.

A study separating the time of dosing of fosamprenavir and lopinavir/r by 4 hours or 12 hours was conducted to examine the possibility that a chemical interaction within the gut was causing these negative pharmacokinetic interactions. Although dose separation had a favorable effect on lopinavir exposure (most likely due to the increased amount of ritonavir administered), it did not improve amprenavir exposure.34

The combination of ritonavir-boosted fosamprenavir 700 mg/100 mg bid with lopinavir/r 400 mg/100 mg bid decreased amprenavir exposure in healthy volunteers, to a similar degree (Table 6).

**Table 6.** Effect of double-boosted regimen of fosamprenavir/r plus lopinavir/r on pharmacokinetics.36

<table>
<thead>
<tr>
<th>Trough concentrations</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>↓ 65%</td>
<td>↓ 63%</td>
</tr>
</tbody>
</table>

**Tipranavir/r plus saquinavir, amprenavir, or lopinavir.** The combination of tipranavir/r 500 mg/200 mg bid with saquinavir 1000 mg bid, amprenavir 600 mg bid, or lopinavir 400 mg bid decreased exposure to all three PIs (Table 7).

**Table 7.** Effect of tipranavir/r on saquinavir, amprenavir, and lopinavir pharmacokinetics in double-boosted regimens.37

<table>
<thead>
<tr>
<th>Trough concentrations</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>↓ 81%</td>
<td>↓ 70%</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>↓ 56%</td>
<td>↓ 45%</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>↓ 55%</td>
<td>↓ 49%</td>
</tr>
</tbody>
</table>

The evidence collected to date indicates that double-boosted PI regimens can have potentially favorable or unfavorable pharmacokinetics (Table 8). Due to the paucity of pharmacokinetic data supporting the safety and efficacy of specific regimens in naive or treatment-experienced HIV-infected patient populations, it is highly advisable that therapeutic drug monitoring be utilized when prescribing double-boosted combinations, to ensure that reasonable exposure to antiretroviral drugs is achieved and maintained.

**PI-chemokine Receptor Antagonist Interactions**

CCR5 chemokine receptor antagonists under evaluation as antiretroviral agents for the treatment of HIV infection include maraviroc and vicriviroc. Like the PIs, these drugs are substrates of CYP3A4. In the case of maraviroc, there does not appear to be any clinically relevant inhibition or induction of CYP3A4 itself.41 Changes in drug exposure have been observed when these compounds are combined with other drugs that are inhibitors or inducers.
Table 8. Pharmacokinetic interactions of double-boosted PIs.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Potentially favorable pharmacokinetics**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/r Atazanavir</td>
<td>400 mg/100 mg bid 300 mg qd</td>
<td>1. Atazanavir $C_{\text{max}}$ and AUC similar, ↑ $C_{\text{min}}$ 2. Lopinavir exposure similar to historical controls 38</td>
</tr>
<tr>
<td>Lopinavir/r Saquinavir</td>
<td>400 mg/100 mg 1000 mg bid</td>
<td>1. Lopinavir and saquinavir exhibit synergistic antiviral activity in vitro 31 2. The reformulation of hard-gel saquinavir as a 500 mg tablet has reduced the pill burden from five capsules per day to two tablets per day 27 3. Saquinavir exposure is largely unchanged by lopinavir/r 14</td>
</tr>
<tr>
<td>Lopinavir/r Nelfinavir</td>
<td>400 mg/100 mg 1000 mg bid</td>
<td>1. Nelfinavir $C_{\text{max}}$ and AUC similar, ↑ $C_{\text{min}}$ 2. Lopinavir ↓ 3. Lopinavir/r should not be administered once daily in combination with nelfinavir 14</td>
</tr>
<tr>
<td>Saquinavir/r Atazanavir</td>
<td>1600 mg/100 mg 300 mg qd</td>
<td>1. Saquinavir exposure is substantially increased ($C_{\text{min}}, C_{\text{max}},$ and AUC) 33 2. Hyperbilirubinemia was quite common (33%), but reversible on stopping atazanavir 33 3. Trough concentrations of saquinavir may be insufficient for resistant virus; consider therapeutic drug monitoring in combination with phenotypic resistance testing</td>
</tr>
<tr>
<td>Saquinavir/r Fosamprenavir</td>
<td>1000 mg/100 mg or 200 mg 700 mg</td>
<td>1. Saquinavir exposure was not significantly altered by the addition of fosamprenavir or vice versa 39 2. Trough concentrations of saquinavir may be insufficient for resistant virus; consider therapeutic drug monitoring in combination with phenotypic resistance testing</td>
</tr>
</tbody>
</table>
| **Potentially unfavorable pharmacokinetics**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/r Fosamprenavir</td>
<td>533 mg/133 mg 1400 mg bid</td>
<td>1. Amprenavir $C_{\text{min}}$ concentrations ↓ 42% compared with fosamprenavir/r 700 mg/100 mg bid 23 2. Lopinavir concentrations similar 23 3. The double-boosted regimen was poorly tolerated, with a high incidence of gastrointestinal intolerance 36 4. Optimal dosing unknown</td>
</tr>
<tr>
<td>Lopinavir/r Indinavir</td>
<td>400 mg/100 mg 600 mg or 800 mg bid</td>
<td>1. Similar AUC, ↓ $C_{\text{max}},$ and ↑ $C_{\text{min}},$ of indinavir with 600-mg vs 800-mg dose 14 2. Lopinavir exposure ↓ 40 3. Combination not well tolerated</td>
</tr>
<tr>
<td>Indinavir/r Atazanavir</td>
<td>Contraindicated</td>
<td>1. Increased risk of hyperbilirubinemia 17</td>
</tr>
<tr>
<td>Tipranavir/r Saquinavir Lopinavir Amprenavir</td>
<td>Not recommended</td>
<td>1. Significant ↓ in saquinavir, lopinavir, and amprenavir exposure 37 2. Optimal dosing unknown</td>
</tr>
</tbody>
</table>
of CYP3A4. For example, pharmacokinetic interactions with saquinavir, ketoconazole, efavirenz, and lopinavir/r have been documented. Efavirenz-containing HAART regimens in HIV-infected patients reduced maraviroc exposure by approximately 50%, while lopinavir/r approximately doubled exposure. In a study of healthy volunteers, saquinavir and ketoconazole were found to have even greater effects on plasma concentrations of maraviroc (>3-fold increase in C_{max} and >4-fold increase in AUC). Similarly, a dose-independent boosting of vicriviroc exposure was observed with ritonavir (C_{max} ↑ approximately 500%; AUC ↑ approximately 350%). These data suggest that, if necessary, pharmacokinetic enhancement of CCR5 antagonists with CYP3A4 inhibitors will be possible.

CONCLUSIONS

Pharmacokinetic enhancement with ritonavir can improve the pharmacokinetic characteristics of PIs used in the treatment of HIV infection by increasing plasma trough concentrations and providing more sustained antiviral activity. Importantly, this helps to extend the dosing interval and reduce pill burden. In some cases, double-boosted PIs may also provide favorable pharmacokinetic interactions, although these are difficult to predict. Furthermore, intra- and inter-patient variation is likely a major confounder. Until more data are available, it is advisable to approach double-boosting with caution and to evaluate individual patients regularly with therapeutic drug monitoring. Although ritonavir is the most potent boosting agent identified to date, it is associated with toxicity and adverse effects and is expensive. Although the boosting effects of other drugs used to treat HIV disease (such as ketoconazole) have been evaluated, they have been found to be less potent and have their own toxicity issues. Further studies to identify potent but less toxic boosting compounds are needed.

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Update on Antiretroviral Treatment Failure and the Management of Treatment-Experienced HIV-Infected Patients

Sharon Walmsley, MD

ABSTRACT

Despite advances in the management of persons living with HIV, and the remarkable improvements in morbidity and mortality, treatment failure still occurs. With failure, the virus becomes increasingly resistant not only to the antiretroviral agents to which it has been exposed but also to other agents in the class. Although we are learning more, and the incidence of triple-antiretroviral-class resistance is decreasing overall, these patients remain a challenge to manage. Failure can be detected by a loss of virologic or immunologic control or by the development of new clinical illness. The approaches to the treatment-experienced patient can include strategies to optimize adherence and impair viral fitness, structured treatment interruption, therapeutic drug monitoring to optimize doses and levels, and the use of resistance testing to guide therapy choices. When choosing new agents, one needs to consider pharmacokinetic enhancement, as can be achieved with the boosted protease inhibitors (PIs) and the use of a new class of agent such as the fusion inhibitors. Data from the TORO, RESIST, and POWER studies have shown that the use of a new boosted PI, together with enfuvirtide, can enable a significant proportion of treatment-experienced patients to have an excellent virologic and immunologic response to new combination therapies. Although still a challenge, the treatment-experienced patient can be effectively managed, and the goal of maximal virologic suppression a reality for many.

INTRODUCTION

Highly active antiretroviral therapy (HAART) for the treatment of HIV infection has led to profound reductions in the incidence of mortality due to AIDS-related causes in recent years. For example, the AIDS Therapy Evaluation National AIDS Therapy Evaluation Centre (ATHENA) cohort (Netherlands) of over 3700 patients receiving antiretroviral therapy showed HIV-related mortality was the most probable cause of over half (55%) of the deaths that occurred among participants between 1996 and 2000. However, the incidence of HIV-related mortality in this cohort significantly decreased over time by >80%, from 3.8 to 0.7 per 100 person-years from 1996 to 2000, while the incidence of non–HIV-related mortality during this time period has remained the same. Similar observations were made for the Aquitaine cohort (France, N = 3687) of HAART-treated HIV-infected patients, for whom the annual number of deaths began to decrease in 1996, with death due to an AIDS-defining cause dropping from 83% in 1995/1996 to 72% in 1996/1997 (P <0.01). By 1998/1999, AIDS-defining events were no longer the major cause of death among these individuals, accounting for only 48% of deaths at this time. The death rate among HIV+ participants in another French cohort, the Antiprotease Cohort (APROCO) (N = 1157), who initiated HAART between 1997 and 1998, was compared to that of the French general population. Overall mortality was approximately eight times that of the general population. However, mortality among complete HAART responders (CD4+ cell count >500 cells/µL and viral load <500 copies/mL from 4 months after initiating HAART to last available follow-up) was only five times higher than the general population. A subsequent analysis combining data from both the Aquitaine and APROCO cohorts revealed more encouraging signs of the
improvements that have been achieved in managing HIV infection. These data confirmed the significant decrease over time in the death rate of HIV-infected patients receiving HAART in these cohorts. Although mortality (adjusted for age and gender) was still higher than in the general population, there was no significant difference between the death rate of participants who achieved and maintained a CD4+ cell count >500 cells/µL and a viral load of <10,000 copies/mL (24%), and that of the general population (standardized mortality ratio 1.1, 95% confidence interval [CI], 0.4-2.2).^5

**TREATMENT FAILURE**

Despite the significant progress that has been made in HIV care since the advent of HAART, therapies continue to fail in a large number of cases, generally because of resistance, which is primarily driven by sub-optimal adherence. A number of common reasons given for poor adherence include adverse effects, difficulties taking antiretroviral drug regimens due to excessive pill burden and/or dosing frequency, dietary restrictions, or simply not having available or forgetting to take doses. Large numbers of patients find drug toxicity the major barrier to full adherence. For example, 58% of participants in the Italian Cohort of Antiretroviral-Naive Patients (I.C.O.N.A.) reported toxicity as the reason for discontinuing a first HAART regimen within 2 years of initiation.^5 Other reasons for treatment failure include primary resistance, in which a patient becomes infected with a resistant virus and is subsequently treated with a HAART regimen to which the virus is not susceptible. Primary resistance to at least one drug class of a first-line regimen is reportedly high in some regions where HAART has been made widely available. For example, in the United Kingdom, the prevalence of genotypic primary resistance to at least one drug is estimated to have risen from around 5% in 1998/1999 to 13% in 2002/2003, with 9% of the latter categorized as HIV infections with high-level resistance.^6 Similar trends have been observed in North America, with phenotypic primary resistance in one location reportedly increasing from 10% in 1998/1999 to 16% in 2000/2001.^5 Finally, individual variations in antiretroviral drug metabolism and interactions between drugs may reduce the efficacy of a regimen in some cases, due to unfavorable pharmacokinetic interactions leading to treatment failure.

**Types of Failure**

Treatment failure of antiretroviral-experienced patients may be defined virologically, immunologically, or clinically. Virological failure is the inability to achieve maximal suppression of HIV replication (undetectable viral load <50 copies/mL), or the achievement of maximal suppression followed by virological rebound. Immunological failure denotes the achievement of a very low or undetectable viral load, but the continued decline in CD4+ cell count. Clinical failure of antiretroviral therapy describes the situation in which an individual exhibits disease progression in terms of new, recurrent, or progressing AIDS-related opportunistic infections or HIV-related symptoms such as weight loss, fatigue, and sweats. Clinical failure may be used to monitor antiretroviral treatment efficacy in settings where CD4+ cell count or viral load testing is unavailable.

**Temporal Trends in the Success of HAART**

There is accumulating evidence that in recent years, the incidence of treatment failure among HIV-infected patients initiating antiretroviral therapy has decreased. This improvement has coincided with increasing knowledge of how to control HIV replication, as well as the introduction of new formulations of existing antiretroviral drugs and new drugs with different mechanisms of action.

**Survival benefits of HAART**

Survival benefits of administering prophylaxis for *Pneumocystis carinii* pneumonia (PCP) and *Mycobacterium avium* complex (MAC), as well as sequential HAART therapies, was estimated to have saved nearly 2 million years of life in the United States between 1989 and 2002, using the cost-effectiveness of preventing AIDS complications (CEPAC) model, a widely utilized computer simulation of HIV disease.^9 Per-person survival gains were estimated to have increased from 2.8-3.5 months prior to HAART (1996) to 50 months in 1997-1998, 117 months in 1998-1999 (two sequential effective HAART regimens), and 124 months
in 2000-2002 (three sequential effective HAART regimens).⁹

**Time to initial virological failure to first HAART**

A marked reduction in the probability of virological failure within the first 12 months of initiating HAART was observed over time among participants from five observational HIV clinic cohorts in Europe and Canada, with the proportion steadily decreasing, from 40% in 1996 to 25% in 2002.¹⁰

**Incidence of triple-class antiretroviral drug failure**

The incidence of triple-class antiretroviral drug failure (defined as 120 days with viral load >1000 copies/mL) peaked at 3.7 per 100 person-years in 2000 (95% CI, 2.9-4.8), and then declined to 0.4% (95% CI, 0.2-1.1) in 2003 among a Danish cohort of HIV-infected patients receiving antiretroviral therapy.¹¹ The 7-year cumulative incidence of triple-class failure was stable between 2001 and 2003 at 6.8% (95% CI, 4.8-9.6), while a lower risk of triple-class antiretroviral drug failure was seen after 2001 than in previous years, regardless of when patients initiated HAART.¹¹

**Incidence of antiretroviral drug resistance mutations**

The percentage of samples with any nucleoside reverse transcriptase inhibitor (NRTI) mutation, protease inhibitor (PI) mutation, or ≥1 mutation for all three drug classes has declined from a peak of 79% to 63%, 82% to 74%, and 42% to 32%, respectively, between 1998 and 2004 among >128,000 clinical isolates received for routine drug resistance testing between 1998 and 2004 (Virco).¹²

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**Table 1.** The goals of antiretroviral therapy for treatment-experienced HIV-infected patients.

<table>
<thead>
<tr>
<th>Type of patient</th>
<th>Goals</th>
</tr>
</thead>
</table>
| Limited exposure to antiretroviral therapy | 1. Virologic: maximal,* durable viral suppression  
2. Immunologic: ↑ CD4+ cell count  
3. Clinical: prevention of opportunistic infection/improved QoL |
| Extensive exposure to antiretroviral therapy | 1. Immunologic: ↑ CD4+ cell count  
2. Clinical: prevention of opportunistic infection/improved QoL  
3. Virologic: optimize viral suppression |

*Undetectable viral load.  
QoL = quality of life.

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**TREATMENT GOALS IN THE MANAGEMENT OF TREATMENT-EXPERIENCED PATIENTS**

The physician’s goal is to offer HIV-infected patients an efficacious, durable therapy with a high genetic barrier to resistance. For a patient with minimal exposure to antiretroviral therapy, the first priority is to maximally suppress viral load, while for those with extensive exposure, where this may not be possible, it is to maximally increase CD4+ cell count (Table 1) with the aim to prevent opportunistic infections. Unfortunately, complex pharmacokinetic interactions between combinations of multiple PIs, as well as adverse drug reactions from antiretroviral agents and/or other anti-HIV drugs that may be required to prevent or treat HIV-related diseases, often limit the options for future therapy. These types of limitations are particularly relevant for extensively pre-treated patients who may already have very limited options due to drug resistance. Like all patients facing daily, life-long therapy, HIV-infected patients want medication that is easy to take; i.e., few pills, easy dosing, and no side effects. In clinical practice, when a treatment-naive HIV-infected patient comes to the office, pill burden is often the biggest concern. However, for treatment-experienced patients, pill burden is often less important. What they want is an effective treatment that they can tolerate. Given this, it is most important to define the goals of what you as a physician and your patient hope to achieve.

**STRATEGIC CONSIDERATIONS**

Drug resistance, which emerges in response to sub-optimal therapy, is the principal challenge when effectively managing HIV infection in treatment-experienced patients.
Drug Resistance Testing

Drug resistance testing is recommended to help select active drugs when changing the therapy of HIV-infected patients failing their current antiretroviral regimen. Testing should be performed while the patient is still taking the failing regimen, or within 4 weeks of discontinuing therapy. In short-term evaluations, genotypic resistance testing has been associated with improved outcomes for treatment-experienced patients, although this may not be of general benefit for all patients. Thus, in some cases, therapy selected by the results of drug resistance testing alone may be insufficient to improve outcomes. It is also important to consider results of previous tests, as resistant mutations may be archived in reservoirs that may re-emerge even though they may not be detected on the current resistance test. In the absence of drug pressure, wild-type or unmutated virus, which is more fit, tends to outgrow the resistant strains. Current resistance tests can only detect populations that represent at least 25% of circulating strains.

Pharmacokinetic Enhancement

Pharmacokinetic enhancement of PIs with ritonavir within a given antiretroviral regimen has been demonstrated to be more efficacious than a single PI in treatment-naive patients, and current treatment guidelines recommend considering pharmacokinetic enhancement for patients failing therapy if at least two fully active agents cannot be identified. Recently, the use of double-boosted PIs (two PIs at therapeutic dosages in combination with low-dose ritonavir) to further enhance antiviral activity has become an area of interest. Further, it is important to note that the efficacy of these regimens is difficult to predict, and drug levels are subject to many inter- and intra-individual variables and known and unknown potential drug interactions. As such, therapeutic drug monitoring on an individual basis is highly advisable to evaluate drug exposure levels on a case-by-case basis. There are insufficient clinical data demonstrating a clear benefit of any specific double-boosted PI regimen in extensively pre-treated HIV-infected patients.

Adherence

It is well established that very high adherence is needed to ensure the success of antiretroviral therapy. Notably, recent research has identified the highest risk of developing drug resistance with relatively high (80-90%), but imperfect adherence (any resistance hazard ratio, 4.15, \( P < 0.001 \); multiple resistance hazard ratio, 6.99, \( P = 0.01 \)). Addressing barriers to adherence, particularly for extensively treated patients, increases the likelihood that a new antiretroviral drug regimen will be effective and durable.

Maximizing adherence

There are various ways to help patients maximize adherence to therapy.

Reducing dosing frequency. Selecting a ritonavir-boosted PI can reduce dosing frequency, as boosting has extended dosing intervals, so that some drugs are now available as twice- or once-a-day regimens (Table 2). Since boosting PIs increases trough drug levels, these combinations are less likely to drop below the minimum concentrations required to inhibit viral replication at the end of a dosing interval. This is especially important for patients who harbor viruses with some degree of resistance that could be overcome by higher drug doses. This also means that patients who miss their drugs by a few hours may still maintain adequate plasma drug concentrations. By being more forgiving in this way, boosted regimens allow patients to be more compliant. Boosting PIs has also led to the removal of food restrictions in some cases, for example, with indinavir and atazanavir. Importantly, several pharmaceutical companies are evaluating higher-concentration formulations to further reduce dosing frequency.

Reducing pill burden. A variety of new formulations of individual agents and combinations of antiretroviral agents may be selected to help reduce pill burden (Table 3).

Availability of New Drugs

The pharmaceutical industry continues to actively pursue the quest for new antiretroviral agents for the treatment of HIV infection.
Two drugs that have been recently approved by the Food and Drug Administration are enfuvirtide (T-20, Fuzeon; accelerated FDA approval March 2003) and tipranavir (Aptivus; FDA approval June 2005). In addition, there are several new drugs in phase II or III clinical

### Table 2. Reduced dosing frequency of ritonavir-boosted protease inhibitors (PIs).

<table>
<thead>
<tr>
<th>PI</th>
<th>Dosing regimen for adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir (Agenerase®)</td>
<td>Not available for adult dosing</td>
</tr>
<tr>
<td>Atazanavir (Reyataz®)</td>
<td>qd or bid</td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva®)</td>
<td>bid or qd</td>
</tr>
<tr>
<td>Indinavir (Crixivan®)</td>
<td>bid or qd</td>
</tr>
<tr>
<td>Lopinavir (Kaletra®)</td>
<td>Not available for adult dosing</td>
</tr>
<tr>
<td>Saquinavir hard-gel (Invirase®)</td>
<td>qd or bid</td>
</tr>
<tr>
<td>Saquinavir soft-gel (Fortovase®)*</td>
<td>tid or bid</td>
</tr>
<tr>
<td>Tipranavir (Aptivus®)</td>
<td>Not indicated</td>
</tr>
<tr>
<td><em>Discontinued February 15, 2006.</em></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Reduced pill burden of new formulations of antiretroviral agents.

<table>
<thead>
<tr>
<th>Antiretroviral agent</th>
<th>Formulation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelfinavir</td>
<td>New: 625 mg nelfinav</td>
<td>2 tablets bid</td>
</tr>
<tr>
<td></td>
<td>Traditional: 250-mg tablet</td>
<td>5 tablets bid</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>New: 500-mg tablet</td>
<td>2 tablets bid</td>
</tr>
<tr>
<td></td>
<td>Traditional: 200-mg capsule</td>
<td>5 capsules bid</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>New: 200/50-mg tablet</td>
<td>2 tablets bid</td>
</tr>
<tr>
<td></td>
<td>Traditional: 133.3/33.3-mg capsule</td>
<td>3 capsules bid or 6 capsules qd</td>
</tr>
<tr>
<td>Fosamprenavir vs amprenavir</td>
<td>Fosamprenavir, pro-drug of amprenavir: 700 mg Amrenavir: 150-mg capsule</td>
<td>2 tablets bid</td>
</tr>
<tr>
<td>Fixed-dose combination of emtricitabine/tenofovir vs emtricitabine plus tenofovir</td>
<td>Truvada™: 200/300-mg combination tablet Emtricitabine 200-mg capsule plus tenofovir 300-mg tablet</td>
<td>1 tablet qd</td>
</tr>
<tr>
<td>Fixed-dose combination of abacavir/lamivudine vs abacavir plus lamivudine</td>
<td>Epzicom®: 600/300-mg combination tablet Abacavir 300-mg tablet plus lamivudine 150- or 300-mg tablet</td>
<td>1 tablet qd</td>
</tr>
<tr>
<td>Fixed-dose combination of lamivudine/zidovudine vs lamivudine plus zidovudine</td>
<td>Combivir®: 150/300-mg combination tablet Lamivudine 150- or 300-mg tablet plus zidovudine 300-mg tablet</td>
<td>1 tablet bid</td>
</tr>
<tr>
<td>Fixed-dose combination of abacavir/lamivudine/zidovudine vs abacavir plus lamivudine plus zidovudine</td>
<td>Trizivir*: 300/300/300-mg combination tablet Abacavir 300-mg tablet plus lamivudine 150- or 300-mg tablet plus zidovudine 300-mg tablet</td>
<td>1 tablet bid</td>
</tr>
</tbody>
</table>
trials, including NRTIs, second-generation NNRTIs, PIs, entry inhibitors, an integrase inhibitor, and a maturation inhibitor. The combination of as many active drugs in a regimen that offer a different, or complementary, barrier to resistance makes new drugs especially important in the management of treatment-experienced HIV-infected patients whose drug options are severely limited due to their harboring multidrug-resistant variants.

**Other Considerations**

**Maintenance of reduced viral fitness**

HIV isolates are known to gain viral fitness (relative ability of a virus to replicate under defined circumstances) during disease progression. The rate of this is directly correlated with viral load and the genetic diversity of the viral envelope (V3 loop). It appears that upon initiation of sub-optimal antiretroviral therapy, drug selection pressure leads to the emergence of drug-resistant HIV that exhibits reduced fitness in vitro compared to wild-type virus. For example, this was observed to be the case after initiation of NRTIs (zidovudine, zalcitabine, lamivudine, and didanosine as mono- or double-therapy) in a patient who had been infected with HIV for about 8 years and had characteristics of late-stage disease. Although antiretroviral therapy had no effect on CD4+ cell count or viral load, the dominant HIV variant isolated after exposure to NRTIs was moderately less fit than that prior to therapy. In the case of lamivudine, the development of the M184V mutation is associated with high-level lamivudine resistance. However, residual antiviral activity of lamivudine is known to be sustained even under conditions of sub-optimal therapy in which M184V has most likely evolved. The M184V-resistant variant has been shown to be less fit than the wild type, and continuing exposure to lamivudine to maintain this mutation may be of virological benefit, particularly in a background of zidovudine resistance. More recently, a more modest benefit of enfuvirtide therapy has been demonstrated in which this drug also appears to prevent HIV from replicating as vigorously in the presence of other antiviral agents despite the presence of enfuvirtide-associated resistance mutations. Thus, in some cases, it may be useful to continue antiretroviral drugs in a failing regimen in order to impair viral fitness while waiting for new therapies to become available.

**Structured treatment interruptions (STIs)**

STIs, prior to the use of salvage therapies in the management of extensively treatment-experienced HIV-infected patients, have been proposed as a means to re-select for drug-susceptible HIV, which may subsequently allow a more durable response to salvage therapy. A study of 270 patients with multidrug-resistant HIV randomized to a 4-month STI followed by a change in antiretroviral regimen or to an immediate change in regimen showed that wild-type virus emerged as the predominant virus in 64% of patients undergoing STI, but this was not associated with improved response rates. The potential role of STIs to improve virologic and immunologic outcomes after antiretroviral failure has been controversial, but the majority of the accumulating evidence suggests that they in fact offer no advantage for extensively pre-treated patients. In the same study, CD4+ cell counts were significantly lower during treatment interruption and remained consistently lower than those of patients who switched immediately to a new regimen. Furthermore, disease progression and death were significantly higher among the group of patients who underwent STI than those who did not (16% vs 9%, P = 0.01). More recently, we conducted a randomized study of 134 patients and found that a 12-week STI prior to salvage therapy did not alter the likelihood of achieving and maintaining an undetectable viral load after initiating salvage therapy (Figure 1). Furthermore, after 60 weeks, there was a statistically lower CD4+ cell count increase (+25 CD4+ cells/µL vs +95 CD4+ cells/µL, P = 0.04), an increased number of AIDS-defining events (four vs zero), and an increased number of HIV-associated infections (five vs two) among the patients randomized to STI.
PRINCIPLES FOR SELECTING ANTIRETROVIRAL THERAPY FOR THE TREATMENT-EXPERIENCED PATIENT

Treatment History, Reasons for Failure, and Co-morbidities

The first thing to consider is why the current regimen has failed. It is important to discuss with patients how drug toxicity (with regard to short- and long-term side effects) may be affecting adherence, as well as other difficulties that may have made taking the medication problematic, such as pill burden, dosing frequency, and/or food restrictions. This information will help to identify which of the possible active regimens is the easiest and most tolerable for patients to take.

The second thing to think about in the case of a treatment-experienced HIV-infected patient failing therapy is the treatment history. A drug-resistance test should be performed in order to identify which drugs remain active against the dominant HIV variant, and these results should be used to guide the selection of a virologically active regimen. Results of any previous resistance tests should also be taken into account. It is also important to consider whether or not your patient can wait until one of the new drugs in development becomes accessible, rather than adding a single new active drug that offers only limited gains in CD4+ cell count and viral suppression.

Third, an assessment of any existing co-morbidities is required to ensure there will not be a problem with additive adverse drug side effects or drug interactions, which can limit the utility of some antiretroviral agents.

After thoroughly evaluating the status of your patient and identifying a prioritized list of possible regimens, the final consideration is cost and insurance coverage. In some cases, costs may be prohibitive.

New Agents With an Active Partner

When a boosted PI is suitable for treatment-experienced HIV-infected patients, an important question is which boosted PI regimen to choose and whether or not to include enfuvirtide in the regimen, or to preserve it for a later time. The efficacy of adding enfuvirtide to an optimized background regimen including a boosted PI in treatment-experienced HIV-infected patients has been evaluated in three large clinical trials. These include the T-20 versus Optimized Regimen Only (TORO) studies (enfuvirtide), the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies (tipranavir/r), and the Performance Of TMC114/r. When evaluated in

![Figure 1. Cumulative percentage of patients achieving viral load <50 copies/mL for at least 3 months.](image)
3-class-Experienced patients with PI Resistance (POWER) studies (TMC114/r). All three studies have demonstrated that enfuvirtide improves virological suppression when added to an active boosted PI in triple-class antiretroviral-experienced patients (Figure 2). These encouraging results suggest that by using more than one new antiretroviral drug, significant (if not maximal) suppression of viral load can be achieved and maintained for more than 24 weeks in a large proportion of extensively treatment-experienced HIV-infected patients who are failing their current regimen.

New agents have shifted the paradigm and have allowed many extensively treatment-experienced patients to achieve maximal viral load suppression if new drug combinations are chosen carefully.

These data suggest that the immunological and virological benefits of new antiretroviral drugs for treatment-experienced HIV-infected patients are maximized by using the drugs together rather than sequentially. The goal for treatment-experienced patients is to preserve the immune system as much as possible for as long as possible in order to prevent onset of HIV-related disease. To achieve this, it is necessary to optimize the reduction in viral load. With this in mind, holding drugs back to preserve future options in case of failure may not be the best approach. Rather, to maximize the immunological and virological response to therapy, we need to use as many new active drugs simultaneously as possible, select new drugs with non-overlapping resistance profiles whenever possible, and add a new agent from a new class whenever possible.

CONCLUSIONS

When a patient presents with virological failure, it is important to review the antiretroviral history in terms of which agents have been used, and to identify which ones failed and why. Particular emphasis should be placed on adverse events, difficulties adhering to the regimen, and drug resistance. Therapy history and drug-resistance test results should be used to inform the choice of any remaining active drugs that are currently available. This, together with knowledge of new agents that may be available within the next year or two, can be used to define and optimize new salvage therapies and the best time to change them. Despite the chronic nature of HIV disease, there is great potential for effectively managing treatment-experienced patients in the future.

Figure 2. New agents work better with an active partner.25
REFERENCES


INTRODUCTION

Many of the recent gains in reduced morbidity and mortality of treatment-experienced HIV patients have occurred as a result of improved dosing and tolerability of existing antiretroviral agents, which have made it easier to successfully control HIV replication. Nevertheless, the continuing need for new agents that are active against drug-resistant HIV is clear. Pharmaceutical companies continue to focus on this goal, with the result that two new drugs have been approved in the last 2 years. Enfuvirtide (T-20) is the first fusion inhibitor to be approved, and tipranavir is a novel non-peptidic protease inhibitor (PI). In addition, a variety of drugs have been or are being evaluated in phase II and III clinical trials, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and PIs as well as agents from new drug classes including entry inhibitors, integrase inhibitors, and maturation inhibitors.

RECENTLY APPROVED ANTIRETROVIRAL AGENTS

Enfuvirtide

This fusion inhibitor is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients failing therapy. Enfuvirtide prevents viral fusion with host cells by binding to glycoprotein gp41 in the HIV envelope. Although enfuvirtide has been available for almost 3 years, relatively few physicians have extensive clinical experience with it, so it will be considered a new drug for the purposes of this review.

The safety and efficacy of enfuvirtide have been demonstrated in the T-20 Versus Optimized Background Regimen Only (TORO 1 and TORO 2) trials in HIV-infected patients experienced with all three available classes of antiretroviral agents (NRTIs, NNRTIs, and...
TORO trials: study design

Participants were randomized 1:2 to either an optimized background regimen alone (three to five antiretroviral agents) selected by the clinical investigator based on genotypic and/or phenotypic drug resistance test results, or an optimized background regimen plus enfuvirtide (90 mg subcutaneous, bid). A switch in therapy was permitted at virological failure or for toxicity reasons.

TORO trials: efficacy and safety

The pooled intent-to-treat population from the two TORO studies comprised 995 patients (661 in the enfuvirtide groups and 334 in the control arm). The proportion of patients with improved virological outcomes was significantly higher in the enfuvirtide group compared with the control group (Figure 1). Furthermore, more than 65% of patients who responded at week 24 maintained their response at week 48.

With regard to safety, most patients in the trials experienced at least one antiretroviral drug-related adverse event during the 48-week study period, excluding local injection site reactions. However, the overall number of treatment-related adverse events was lower among those randomized to enfuvirtide than to the control group (96.2 events vs 149.9 events per 100 patient-years), and more patients in the control group than in the enfuvirtide group discontinued study therapy before 48 weeks (37% vs 26%). Injection site reactions occurred in almost all (98%) enfuvirtide-treated participants and accounted for approximately 4% of discontinuations in this group. The proportion of patients experiencing pain or discomfort with enfuvirtide injection remained steady throughout the treatment period, with 46-53% reporting mild tenderness, 15-20% reporting moderate pain and 1-3.5% reporting severe pain requiring analgesics or limiting usual activities; injection site reactions typically lasted for 3-7 days. The most frequent signs and symptoms of injection site reactions were pain and/or discomfort, erythema, and induration, which occurred in over 90% of cases, while nodules and cysts developed in 80% of cases.

Figure 1. The TORO trials: efficacy of enfuvirtide (ENF) plus optimized background (OB) versus OB alone in intent-to-treat population.
Summary

These data show a significant benefit of enfuvirtide in treatment-experienced patients. Unfortunately, because it is administered twice daily by injection, it is a difficult drug to take consistently. This and cost are currently the principal barriers to its more widespread use. A recent evaluation of a Biojector needle-free gas-powered injection device as an alternative delivery system has shown that plasma levels of enfuvirtide are similar after administration with the Biojector or needles. Importantly, the Biojector device reduced symptoms of injection site reactions by approximately 50% compared to needles, and on average, patients found it easier to use than needles. Thus, this delivery method may extend the clinical utility of enfuvirtide. Interestingly, the next generation of fusion inhibitors includes two candidates that demonstrate substantial improvements in potency, durability, and pharmacokinetics that may enable the evaluation of sustained-release formulations at once-weekly dosing.

Tipranavir

A non-peptidic HIV PI, tipranavir became available in 2005 for use in combination with ritonavir (r) in treatment-experienced HIV-infected patients. The unique binding interactions of tipranavir with HIV protease make it active against a substantial range of HIV variants that are resistant to other PIs. Furthermore, it appears that multiple PI mutations may be required before any significant loss in susceptibility to tipranavir occurs.

The safety and efficacy of tipranavir have been demonstrated in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir trials (RESIST 1 and RESIST 2) in HIV-infected patients with triple-class failure, failing their current HAART regimen. RESIST 1 was conducted in North America and Australia, while RESIST 2 was conducted primarily in Europe.

RESIST trials: study design

The study design of the RESIST trials was similar to that described above for the TORO trials, i.e., optimized background (including a comparator-boosted PI) versus optimized background plus tipranavir in place of the comparator PI.

RESIST trials: efficacy and safety

A pooled analysis of RESIST 1 and 2 showed that adding tipranavir/r to an optimized background regimen increased the proportion of patients achieving a viral load of <400 copies/mL after 48-weeks (30% vs 14% for patients who received optimized background regimen alone, \(P < 0.0001\)). This demonstrated the durability of the treatment response for the majority of patients who achieved <400 copies/mL by 24 weeks (35% vs 17%). In a combined analysis of data from RESIST 1 and 2, the CD4+ cell response at 48 weeks was significantly higher among patients who received tipranavir/r (+45 cells/µL vs +21 cells/µL, \(P < 0.001\)). With regard to safety, tipranavir/r was associated with increased grade 3/4 liver enzyme levels (alanine transaminase 9.7% vs 4.2% and aspartate transaminase 6.1% vs 1.8%) and lipid levels, particularly cholesterol and triglycerides (2.1% vs 0.4% and 24.9% vs 13.0%, respectively), compared to patients on comparator-boosted PIs.

Summary

Adding tipranavir/r to an optimized background regimen can provide a durable virological response in treatment-experienced patients, particularly in combination with other active agents, such as enfuvirtide (52% of patients with first-time enfuvirtide use achieved <400 copies/mL by 48 weeks compared to 20% of control group). A limitation of tipranavir is its association with liver toxicity; therefore, liver function tests should be performed prior to initiating therapy with tipranavir and periodically during treatment. It can be administered to patients with hepatitis B and/or C, although extra diligence with regard to monitoring for hepatotoxicity is recommended for these patients, as they are at heightened risk of liver toxicity. Tipranavir is contraindicated for those with moderate to severe hepatic insufficiency (Child-Pugh Class B and C).
ANTIRETROVIRAL AGENTS IN CLINICAL TRIALS

PIs

TMC114 (darunavir), a new PI developed by Tibotec (Belgium), was designed to be active against HIV resistant to currently available PIs. A phase IIA proof-of-principle trial showed that ritonavir-boosted TMC114 (TMC114/r) had potent short-term antiviral activity in HIV-infected patients with high-level PI resistance. Upon replacing PIs in a failing regimen with TMC114/r, a decrease in plasma HIV RNA of \( \geq 1.0 \log_{10} \text{copies/mL} \) was attained by 76% of patients (mean of three groups on different doses of TMC114/r) compared with only 17% of a control group. A viral load of \(<400\) copies/mL was achieved by 40% of patients receiving TMC114/r versus 8% of control patients. A single case of hepatotoxicity was reported in this trial, which resolved upon the discontinuation of highly active antiretroviral therapy (HAART).

TMC114/r has subsequently been evaluated in phase IIB trials known as the Performance Of TMC114/r When evaluated in 3-class-Experienced patients with PI Resistance (POWER) trials (POWER 1 and POWER 2). POWER 1 was conducted in Europe, Australia, Brazil, and Canada, while POWER 2 was conducted in the United States. These studies evaluated four doses of TMC114/r in triple-class-experienced patients, with evidence of at least one primary PI resistance mutation.

**POWER trials: study design**

The study design for the POWER trials was essentially as described earlier for the TORO and RESIST trials, except that four different doses of TMC114/r (400/100 mg once daily, 800/100 mg once daily, 400/100 mg bid, 600/100 mg bid) were evaluated versus an optimized background regimen alone.

**POWER trials: efficacy and safety**

A week 24 interim analysis of POWER 1 showed that a significantly higher percentage of patients receiving TMC114/r at the highest dose (600/100 mg bid) achieved a viral load reduction from baseline of \( >1.0 \log_{10} \text{copies/mL} \) compared to the optimized background regimen alone (77% vs 25%, \( P < 0.001 \)), and mean CD4+ cell count increases were significantly higher in the TMC114/r group than in the control group (+124 cells/\( \mu \text{L} \) vs +20 cells/\( \mu \text{L} \)). As with tipranavir/r, the antiviral effect of TMC114/r was improved by concomitant use of enfuvirtide, although the magnitude of the difference in POWER 1 was quite modest (63% of patients receiving enfuvirtide plus TMC114/r [600/100 mg bid] achieved a viral load of \(<50\) copies/mL, compared with 56% of patients who did not receive enfuvirtide in the optimized background regimen). The most commonly reported adverse events among patients receiving TMC114 were headache, diarrhea, nausea, insomnia, and fatigue, the frequency of which was not dose-dependent or significantly higher than reported for the control group. No significant liver abnormalities occurred with TMC114/r during the first 24 weeks of follow-up. A week 24 interim analysis of POWER 2 showed similar results: 62% of patients in the TMC114/r (600/100 mg) group achieved virological response (\( >1 \log_{10} \text{copies/mL} \) reduction in viral load), versus 14% of the control group. Mean CD4+ count increases were +59 cells/\( \mu \text{L} \) in the TMC114/r group versus +12 cells/\( \mu \text{L} \) in the control group. Patients in the TMC114/r group also reported the same most common adverse events as in POWER 1 (insomnia, headache, fatigue, nausea, and diarrhea), which were of mild-to-moderate severity, not dose-dependent, and comparable to the control group.

**Summary**

Adding TMC114/r to an optimized background regimen represents a promising new alternative for treatment-experienced patients with PI resistance who are failing therapy, particularly when it is added with another active antiretroviral agent such as enfuvirtide. In contrast to tipranavir/r, TMC114/r did not show an association with liver toxicity, and may therefore be a better option for patients co-infected with hepatitis B and/or hepatitis C virus, although head-to-head comparisons have not been done.

NRTIs and NNRTIs

**Reverset (dexelvucitabine, D-D4FC)**

This NRTI has in vitro activity against HIV isolates resistant to other NRTIs, including zidovudine and lamivudine, and has shown...
potent antiretroviral activity in vivo in phase I trials (mean viral load decrease of approximately 1.6 log\textsubscript{10} HIV RNA copies/mL).\textsuperscript{17} Despite these promising initial results, a review by the Food and Drug Administration of phase II data concluded that the viral load changes in these studies were insufficient to support proceeding to phase III trials. The development program for this drug was discontinued in April 2006.

Amdoxovir (DAPD)

The development program for this drug was discontinued in April 2006. This NRTI showed good antiviral activity against HIV isolates with mutations associated with resistance to other NRTIs,\textsuperscript{18} as well as antiviral activity in treatment-naive and treatment-experienced HIV-infected patients (median decreases of 1.5 log\textsubscript{10} HIV RNA copies/mL and 0.7 log\textsubscript{10} HIV RNA copies/mL, respectively).\textsuperscript{19} Unfortunately, additional studies did not support its role in treating patients with resistant HIV infections, and it is not currently in active clinical development.

Tibotec is developing two NNRTIs known as TMC125 (etravirine) and TMC278. Both of these drugs are being evaluated in clinical trials. TMC125, a diarylpyrimidine derivative, is highly active against wild-type HIV and retains significant activity (EC\textsubscript{50} <10 nM) against a majority (77%, compared to only 23% for efavirenz) of clinical isolates resistant to at least one of the currently available NNRTIs (delavirdine, efavirenz, and nevirapine).\textsuperscript{20} Administration of this drug in a phase IIA monotherapy trial in antiretroviral-naive patients resulted in a significant reduction in viral load compared to placebo (1.99 log\textsubscript{10} copies/mL vs 0.06 log\textsubscript{10} copies/mL P <0.001), after 7 days of therapy.\textsuperscript{21} TMC125 has subsequently been evaluated in a phase IIB trial of HIV-infected patients failing an NNRTI-containing (efavirenz or nevirapine) HAART regimen and with evidence of NNRTI resistance. Substituting TMC125 for the NNRTI in the failing regimen was associated with a median viral load decrease of 0.89 log\textsubscript{10} copies/mL, after 7 days of treatment.\textsuperscript{22} A phase II dose-finding study of TMC125 also demonstrated potent antiviral activity of this agent in heavily pre-treated patients with substantial NNRTI and PI resistance compared to a standard-of-care regimen, at 24 weeks.\textsuperscript{23} However, it is worth noting that another, similar phase II study of TMC125 efficacy in HIV-infected patients with NNRTI resistance was stopped early due to a poorer antiviral response than that of the control group. The reasons for these inconsistencies are not yet clear. To overcome the low solubility and permeability of TMC125, several new formulations using hydroxypropyl methylcellulose (a polymeric emulsifier) have been developed. Test formulations showed a marked increase in relative oral bioavailability that will allow a reduced pill burden in phase III trials, which are now under way (DUET 1 and 2).\textsuperscript{24} These trials will evaluate the safety and efficacy of a combination of two experimental drugs, namely TMC125 and TMC114.

TMC278, another diarylpyrimidine derivative from Tibotec, has also exhibited good antiretroviral activity in a phase IIA trial of antiretroviral-naive patients (viral load decreases of >1.0 log\textsubscript{10} copies/mL).\textsuperscript{25} TMC278 has been shown to provide an increased barrier to resistance compared to existing NNRTIs, and a good safety profile and pharmacokinetic profile that facilitates its development as a once-daily regimen.\textsuperscript{26}

Entry Inhibitors

One of the major targets for new classes of antiretroviral agents is HIV entry (Figure 2). The first drug approved that inhibits viral entry was enfuvirtide, which prevents the fusion of the viral envelope and CD4+ cell membrane by interfering with the gp41 viral helical bundle formation. Another approach to preventing viral entry is to block virus interaction with the chemokine co-receptors (CXCR4 and CCR5) that are required for successful viral entry. Three CCR5 co-receptor antagonists have entered clinical trials to date: aplaviroc (GlaxoSmithKline), vicriviroc (Schering-Plough), and maraviroc (Pfizer).

Aplaviroc (873140)

This drug demonstrated prolonged binding to the CCR5 receptor with a half-life of approximately 5 days, and exhibited sustained viral suppression for up to 48 hours after therapy discontinuation.\textsuperscript{28} Aplaviroc exhibited potent antiviral activity in a mixed group of treatment-naive and -experienced HIV infected
patients, with all subjects achieving >1 log$_{10}$ copies/mL reduction in viral load at all doses.$^{29}$ Unfortunately, phase III trials of aplaviroc in antiretroviral-naive patients were discontinued in September 2005 due to liver toxicity, including two emergent cases of drug-related severe hepatotoxicity. Enrollment of treatment-experienced patients has been stopped and the development program for aplaviroc terminated.$^{30}$

**Vicriviroc (SCH-D)**

This compound reduced viral load in a dose-dependent fashion by approximately 1.0-1.6 log$_{10}$ copies/mL in phase II trials.$^{31}$ Phase II trials of vicriviroc in treatment-naive patients were initiated but subsequently discontinued due to poor virologic control relative to the control group receiving efavirenz.$^{32}$ Treatment-naive patients were randomized to receive vicriviroc (25, 50, or 75 mg once daily) or placebo. After 14 days, co-formulated lamivudine/zidovudine was added, and efavirenz replaced placebo in the control group. At 2 weeks, vicriviroc showed a significantly greater decrease in viral load from baseline compared to placebo ($P<0.001$ for each vicriviroc arm vs placebo), but at the time the study was closed, the rate of virologic breakthrough (RNA $\geq$50 copies/mL) was 8% in the control group versus 57%, 45%, and 22% for the 25, 50, and 75 mg doses of vicriviroc, respectively ($P<0.001$ for the pooled vicriviroc arms versus control). Virologic rebound was associated with the presence of the M184V mutation for lamivudine resistance.$^{33}$ The phase II study of vicriviroc in treatment-experienced patients is continuing in a study being conducted by the National Institutes of Health-sponsored Adult AIDS Clinical Trials Group (ACTG). In March, the ACTG Study Monitoring Committee reported that five cases of cancer (four cases of lymphoma and one of gastric adenocarcinoma) were detected in treatment-experienced patients on vicriviroc. However, a causal relationship was not shown, and as of March 3, 2006, the study was to continue.$^{34}$

**Maraviroc (UK-427,857)**

Early studies of maraviroc have shown good tolerability and potent antiviral activity in HIV-positive patients, resulting in mean reductions in viral load of 1.60 (300 mg once daily) and 1.84 (300 mg bid) log$_{10}$ copies/mL after 10 days of therapy.$^{35}$ Further evaluation indicated that doses of 100 mg or more resulted in viral load reductions of $\geq 1$ log$_{10}$ copies/mL when given as short-term monotherapy either once daily or twice daily.$^{36}$ The most common treatment-associated adverse events were headache, dizziness, nausea, asthenia, flatulence, and rhinitis, and the adverse event profile was similar to that of placebo.$^{35}$ Phase II trials of maraviroc were initiated and are ongoing in treatment-naive and -experienced HIV-infected patients. It should be noted that discontinuation of the once-daily maraviroc (300 mg) phase III treatment arm in antiretroviral-naive subjects was recommended by Pfizer’s independent
data safety monitoring board in January 2006, due
to failure to meet pre-specified non-inferiority
criteria. However, maraviroc remains the most
promising first drug of this class to date.

**Integrase Inhibitors**

Integrase inhibitors exert their antiviral effect by preventing HIV integrase from catalyzing the integration of HIV derived from viral DNA into the host cell chromosome DNA via an effect on strand transfer. This potently inhibits HIV replication. Two HIV integrase inhibitors have advanced to clinical trials.

**MK-0518**

This integrase inhibitor is under development by Merck & Co. It has potent in vitro activity against HIV and good bioavailability in healthy volunteers. A dose-ranging study of MK-0518 in HIV-infected patients showed MK-0518 to be very well tolerated and resulted in viral load reductions of 1.7 to 2.2 log_{10} copies/mL after 10 days of monotherapy, with at least 50% of patients achieving a viral load of <400 copies/mL. A dose-ranging evaluation of MK-0518 in combination with an optimized background regimen versus an optimized background regimen alone in treatment-experienced HIV-infected patients resulted in 63% to 67% of patients receiving MK-0518, versus 8% in the control group achieving a viral load of <50 copies/mL, while 85% to 92% versus 24% achieved viral load <400 copies/mL.

**GS-9137 (JTK-303)**

This drug, being developed by Gilead Sciences, is also a potent inhibitor of HIV integrase. A 10-day dose-ranging study in a mixed group of antiretroviral-naive and -experienced patients demonstrated GS-9137 to be well tolerated at all dosages tested. A dose-dependent median decrease in viral load was observed, ranging from 1.48 log_{10} copies/mL when administered alone (200 mg bid), to 2.03 log_{10} copies/mL when boosted with ritonavir (50 mg/100 mg once daily). This drug is about to enter into large-scale phase II clinical trials. In contrast to MK-0518, GS-9137 is a cytochrome P (CYP) 3A4 substrate, and its pharmacokinetics are significantly affected by ritonavir or other inhibitors of CYP3A4.

**ANTIRETROVIRAL AGENTS IN EARLY DEVELOPMENT**

**Maturation Inhibitors**

HIV maturation inhibitors exert their antiviral effect by blocking processing of the Gag proteins. This inhibits normal viral maturation and HIV infectivity.**

**PA-457**

This agent is a potent inhibitor of HIV replication in vitro, including the replication of isolates resistant to reverse transcriptase inhibitors and PIs. As noted, its mechanism of action includes creating defects in Gag processing that prevent cleavage of the capsid pre-protein p25 to the mature capsid protein p24. As a consequence, new HIV virions released from host cells are rendered non-infectious. PA-457 has been found to be well tolerated and suitable for once-daily oral dosing, which at the highest dose (250 mg) tested resulted in a dose-dependent median reduction in viral load of 0.51 log_{10} copies/mL, compared to 0.17 log_{10} copies/mL for placebo (P <0.05).

Although this drug appears to have less potent activity than the integrase inhibitors or the CCR5 antagonists, it may offer considerable value in extensively treatment-experienced patients with multiclass resistance.

**CONCLUSIONS**

Today, the availability of over 20 antiretroviral agents has transformed HIV infection into a chronic manageable disease, and many infected individuals appear likely to be able to live longer and healthier lives. However, multiple factors may limit the value of antiretroviral therapy, particularly for patients who have been on therapy for many years. For extensively treated patients who are failing therapy, new drugs, particularly those targeting new steps in the viral replication process, offer new therapeutic opportunities and considerable promise for the future.
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