Optimizing Adherence to Highly Active Antiretroviral Therapy: A Focus on Fosamprenavir

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INTRODUCTION
Advances in antiretroviral therapy over the past decade have improved the management of human immunodeficiency virus-1 (HIV-1) infection. Currently, the principal goals of antiretroviral pharmacotherapy require continuous drug therapy (1) to ensure maximal and prolonged suppression of viral loads, (2) to restore CD4 lymphocyte cell counts, (3) to improve quality of life, and (4) to reduce morbidity and mortality related to HIV infection and acquired immunodeficiency syndrome (AIDS).1

Therapeutic success and efficacy ultimately depend on patient adherence to antiretroviral therapy that produces minimal side effects and offers simple dosing regimens.2 However, success with available protease inhibitors is limited by several factors, including complicated dosing schedules and intolerable side effects.3

In general, protease inhibitors (PIs) are well known for their metabolic adverse drug effects (ADEs) such as lipid abnormalities, impaired glucose tolerance, insulin resistance, and an increased risk of lipodystrophy. Gastrointestinal (GI) side effects (e.g., drug intolerance, nausea, vomiting, and diarrhea) are also characteristic of this drug class.4 All of the aforementioned ADEs make it difficult for patients to adhere to antiretroviral regimens. Poor compliance with any combination therapy that includes a PI is likely to result in an increased risk of emerging PI-resistant variants and treatment failure.5 In general, poor compliance with highly active antiretroviral therapy (HAART) has significant consequences, including:5

- continuous viral replication.
- increased viral resistance.
- development of clinical complications.
- reduced survival.

Several studies have concluded that greater than 95% adherence is required to achieve adequate therapeutic responses.5 In 1999, amprenavir (Agenerase®, GlaxoSmithKline) was the fifth PI to be approved by the Food and Drug Administration (FDA). Current HIV treatment guidelines do not advocate the use of amprenavir as the sole PI in patients, partly because of concerns of a high pill burden (16 capsules/day) and the potential for poor compliance.

On October 21, 2003, the FDA approved yet another PI, a prodrug of amprenavir—fosamprenavir calcium (Lexiva™, GlaxoSmithKline/Vertex)—in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. Fosamprenavir was evaluated in two major clinical trials to determine its efficacy, safety, and potential benefits when used in a PI-based regimen.

PHARMACOLOGY
After administration, fosamprenavir is rapidly hydrolyzed to amprenavir and inorganic phosphate by cellular phosphatases as it is absorbed by the gut epithelium. Its pharmacology is similar to that of amprenavir.6 Amprenavir inhibits HIV-1 protease by binding to the enzyme’s active site.7 HIV-1 protease enzyme is required for the cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Thus, by inhibiting this enzyme, amprenavir prevents the processing of viral Gag and Gag-pol polyprotein precursors. The result is the formation of immature and noninfectious viral particles.8

PHARMACOKINETICS
The pharmacokinetic properties of fosamprenavir have been evaluated in healthy adult volunteers and in HIV-infected patients (Table 1). Fosamprenavir undergoes rapid hydrolysis to amprenavir and inorganic phosphate before entering the systemic circulation.8 After oral administration of a single dose of fosamprenavir, the time to peak concentration (T_{max}) of amprenavir occurs between 1.5 and four hours. The plasma elimination half-life (T_{1/2}) is 7.7 hours.

Amprenavir is 90% protein-bound in vitro and is metabolized in the liver by cytochrome P450 3A4 (CYP3A4). Along with its glucuronide conjugates, amprenavir is minimally eliminated in the urine and feces.8 Because less than 1% of the administered dose is eliminated unchanged, a dosage adjustment would be unnecessary in patients with renal insufficiency.

Wood et al.6 evaluated the pharmacokinetics of fosamprenavir and amprenavir following repeated dosing in patients with HIV-1 infection. The study compared the amprenavir area-under-the-concentration time curve (AUC) during...
a dosing interval, the minimum concentration at the end of a dosing interval at steady state ($C_{\text{min,ss}}$), and the maximum concentration at steady state ($C_{\text{max,ss}}$) with those of amprenavir in combination with GlaxoSmithKline’s abacavir (Zia- gen®) and lamivudine (Epivir®). The authors concluded that both fosamprenavir and amprenavir delivered equivalent plasma drug concentrations. The pharmacokinetics of amprenavir has also been evaluated in patients with hepatic insufficiency. Unlike healthy adult volunteers, patients with moderate-to-severe hepatic impairments had AUC and $C_{\text{max}}$ amprenavir concentrations that were significantly higher: $12 \pm 4.38 \text{ mcg • hour/ml}; 4.90 \pm 1.39 \text{ mcg • hour/ml}$ versus $38.66 \pm 16.08 \text{ mcg • hour/ml}; 9.43 \pm 2.61 \text{ mcg • hour/ml}$. Subsequently, dosages might need to be adjusted in this patient population.

No data are available on the use of boosted fosamprenavir in patients with any hepatic impairment.

**CLINICAL TRIALS**

Clinical trials on the safety and efficacy of fosamprenavir in HAART-naïve infected patients have been extensively published.8–11

**The NEAT Trial**
The NEAT study was a 48-week, multicenter, open-label comparative study. To evaluate the safety and efficacy of fosamprenavir versus nelfinavir (Viracept®, Agouron), investigators enrolled 249 HAART-naïve adults with a plasma HIV-1/RNA of 5,000 or more copies/ml at screening. In a 2:1 ratio, patients were assigned either fosamprenavir or nelfinavir for a minimum of 48 weeks in addition to abacavir and lamivudine.

In 166 patients receiving fosamprenavir (1,400 mg twice daily), 66%—compared with 51% of the 83 patients taking nelfinavir (1,250 mg twice daily)—achieved a viral load below 400 copies/ml. Furthermore, 55% of the patients receiving fosamprenavir achieved a viral load of fewer than 50 copies/ml, compared with 41% of the nelfinavir patients. The percentage of patients experiencing virological failure was higher in the nelfinavir group (28%) than in the fosamprenavir group (14%). In both groups, the incidence of dose-limiting ADEs and laboratory abnormalities was insignificant, except for diarrhea, which was more common in the nelfinavir group (18%) than in the fosamprenavir group (5%).9

**The SOLO Trial**
The SOLO trial evaluated the safety and efficacy of fosamprenavir boosted with ritonavir (Norvir®, Abbott) versus nelfinavir for 48 weeks. In this open-label study, 649 HAART-naïve patients were randomly selected, in a 1:1 ratio, to receive fosamprenavir 1,400 mg/ritonavir 200 mg daily or nelfinavir 1,250 mg twice daily in combination with abacavir and lamivudine. The results revealed comparable efficacy; 68% of patients receiving the combination and 65% of those receiving nelfinavir achieved an undetectable HIV-1/RNA level (fewer than 400 copies/ml). Fifty-six percent of the fosamprenavir/ritonavir patients, compared with 52% of the nelfinavir patients, achieved a viral load below 50 copies/ml.10 Although no discernible differences in efficacy and tolerability were seen among the groups, the results of this study confirmed the added benefit of a low pill burden.

**The CONTEXT Trial**
CONTEXT, a phase III, randomized, open-label, non-inferiority study, was conducted to compare the antiviral response of patients receiving two different dosing regimens of boosted fosamprenavir with that of patients receiving lopinavir/ritonavir (Kaletra®, Abbott) at 24 and 48 weeks, respectively. The primary endpoint of the trial was the mean time average change in plasma HIV-1/RNA levels at baseline to week 24 in 315 PI-experienced patients. For all of the patients, therapy had been unsuccessful with their current regimen.

The patients were randomly selected, in a 1:1:1 ratio, to receive fosamprenavir 1,400 mg/ritonavir 200 mg once daily, fosamprenavir 700 mg/ritonavir 100 mg twice daily, or lopinavir 400 mg/ritonavir 100 mg twice daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) that were selected on the basis of resistance testing. From the baseline evaluation to week 24, the time-averaged changes in HIV-1/RNA were $-1.46 \log_{10} \text{ copies/ml}$ for the fosamprenavir/ritonavir once-daily arm, $-1.48 \log_{10} \text{ copies/ml}$ for the fosamprenavir/ritonavir twice-daily arm, and $-1.63 \log_{10} \text{ copies/ml}$ for the lopinavir/ritonavir twice-daily arm. The median CD4 cells/mm² changes from baseline were 72 for once-daily fosamprenavir/ritonavir, 62 for twice-daily fosamprenavir/ritonavir, and 63 for twice-daily lopinavir/ritonavir.11 Thus, after 24 weeks, the investigators concluded that boosted fosamprenavir was equivalent to lopinavir/ritonavir.

**DRUG RESISTANCE**
Analysis of viral isolates identified mutational patterns of unboosted fosamprenavir. Protease mutations were consistent with the amprenavir profile. In
patients who were experiencing virological rebound after treatment with unboosted fosamprenavir, clinical isolates containing mutations at positions V32I, I47V, 154L/M, I50V, M46I/L, and I84V were identified.7,9,12 Mutations were also identified in the p7/p1 and p1/p6 Gag and Gag-Pol polyprotein precursor cleavage sites. The HIV clinical isolates with mutational patterns retained sensitivity to lopinavir, saquinavir (Fortovase®, Invirase®, Roche), and boosted indinavir (Crixivan®, Merck).12

ADVERSE DRUG EFFECTS

In clinical trials, the most commonly reported ADEs associated with the use of fosamprenavir were nausea, vomiting, diarrhea, headache, and rash (Table 2).9 These ADEs were usually described as mild to moderate in severity and did not require discontinuation of the drug. During clinical trials, only 6.4% of patients stopped drug therapy as a result of ADEs. Although 19% of the fosamprenavir patients experienced mild skin reactions, only one case of a severe, life-threatening dermatological effect, such as Stevens–Johnson syndrome, was reported.7

DRUG INTERACTIONS

Amprenavir, the active metabolite of fosamprenavir, is an inhibitor of CYP3A4 metabolism. Therefore, the concurrent administration of fosamprenavir and drugs that induce this isoenzyme, such as barbiturates, phenytoin, and rifampin, may decrease amprenavir concentrations and, ultimately, may reduce therapeutic efficacy. In contrast, when coadministered with CYP3A4 inhibitors, such as ketoconazole (Nizoral®, Janssen), verapamil (e.g., Calan®, Pfizer), and sertraline (Zoloft®, Pfizer), amprenavir concentrations, as well as the incidence of ADEs, may increase. To prevent the loss of virological response, resistance to fosamprenavir, or resistance to the class of PIs, prescribers should avoid coadministration of fosamprenavir and delavirdine (Rescriptor®, Agouron/Pfizer) or rifampin (Table 3).7

PRECAUTIONS AND CONTRAINDICATIONS

Fosamprenavir should be used with caution in patients with sulfa allergy, hepatic impairment, hemophilia, immune reconstitution, fat redistribution, and lipid elevations. This agent is contraindicated in patients with clinically significant hypersensitivity to any components of this product or to amprenavir. Fosamprenavir is also contraindicated with the coadministration of drugs that require CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious, life-threatening events (see Table 3).7

Table 2 Adverse Events Associated with Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Effect</th>
<th>Fosamprenavir 1,400 mg b.i.d. (n = 166) (%)</th>
<th>Nelfinavir 1,250 mg b.i.d. (n = 83) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Weakness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>


Table 3 Fosamprenavir Drug Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic agents</td>
<td>Flecaïnide® (Tambocor®, 3M), propafenone® (Rythmol®, Abbott)</td>
</tr>
<tr>
<td>Antimycobacterial agents</td>
<td>Rifampin (Rifadin®, Aventis)</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dilhydroergotamine® (Migranal®, Xcel), ergonovine®, ergotamine®, methylergonovine®</td>
</tr>
<tr>
<td>Gastrointestinal motility agents</td>
<td>Casapride® (Propulsid®, Janssen)</td>
</tr>
<tr>
<td>Herbal products</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>HMG–CoA reductase inhibitors</td>
<td>Lovastatin (Mevacor®, Merck), simvastatin (Zocor®, Merck)</td>
</tr>
<tr>
<td>Neuroleptic agents</td>
<td>Pimozide® (Orap®, Gate)</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
<td>Delavirdine (Recriptor®, Agouron)</td>
</tr>
<tr>
<td>Sedative/hypnotic agents</td>
<td>Midazolam® (Versed®, Roche), triazolam® (Halcion®, Pfizer)</td>
</tr>
</tbody>
</table>

* These drugs are contraindicated with the coadministration of fosamprenavir.

HMGC–CoA = 3-hydroxy-3-methylglutaryl–coenzyme A.
Data from Lexiva™ package insert, GlaxoSmithKline.7

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fosamprenavir over amprenavir include a decreased pill burden and a flexible dosing regimen, both of which help to improve compliance. Recommended doses of fosamprenavir, which are based on the patient’s previous use of PIs, are as follows:

- **For therapy-naive patients:**
  - fosamprenavir 1,400 mg twice a day (without ritonavir)
  - fosamprenavir 1,400 mg once a day plus ritonavir 200 mg once a day
  - fosamprenavir 700 mg twice a day plus ritonavir 100 mg twice a day

- **For PI-experienced patients:**
  - fosamprenavir 700 mg twice a day plus ritonavir 100 mg twice a day
  - not recommended for PI-experienced patients: once-daily fosamprenavir/ritonavir

- **Fosamprenavir/ritonavir in combination with efavirenz:**
  - When efavirenz (Sustiva®, Bristol-Myers Squibb) is administered with this combination once daily, an additional 100 mg/day (300 mg total) of ritonavir is recommended.

In patients with mild or moderate hepatic impairment, a reduced dose of fosamprenavir 700 mg twice daily is recommended if they are not receiving concurrent ritonavir. The use of doses below 700 mg is not recommended; therefore, patients with severe hepatic impairment should not use fosamprenavir. Currently, no data are available on the use of fosamprenavir/ritonavir in patients with any degree of hepatic impairment.

### COST

A projected monthly cost of fosamprenavir 1,400 mg twice daily is approximately $960. Table 4 presents a comparison of the estimated monthly cost of fosamprenavir with typical daily doses of other currently available PIs.

### SUMMARY

The advent of HAART has significantly improved the management of patients

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**Table 4  Overview of Protease Inhibitors**

<table>
<thead>
<tr>
<th>Name</th>
<th>Usual Unboosted Adult Daily Dosing</th>
<th>Food Requirement</th>
<th>Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir (Agenerase®, GlaxoSmithKline)</td>
<td>1,200 mg b.i.d. (16 caps/day)</td>
<td>Yes/No</td>
<td>$706.12</td>
</tr>
<tr>
<td>Atazanavir (Reyataz™, Bristol-Myers Squibb)</td>
<td>400 mg q.d. (2 caps/day)</td>
<td>Yes</td>
<td>$808.20</td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva™, GlaxoSmithKline)</td>
<td>1,400 mg b.i.d. (4 tabs/day)</td>
<td>Yes/No</td>
<td>$960.00</td>
</tr>
<tr>
<td>Indinavir (Crixivan®, Merck)</td>
<td>800 mg every 8 hours (6 caps/day)</td>
<td>Yes (one hour before or two hours after meals; no effect when taken with ritonavir)</td>
<td>$546.38</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra®, Abbott)</td>
<td>400/100 mg b.i.d. (6 caps/day)</td>
<td>Yes</td>
<td>$703.50</td>
</tr>
<tr>
<td>Nelfinavir (Viracept®, Agouron)</td>
<td>750 mg t.i.d. (9 tabs/day) or 1,250 mg b.i.d. (4 tabs/day)</td>
<td>Yes</td>
<td>$756.66</td>
</tr>
<tr>
<td>Ritonavir ((Norvir®, Abbott)</td>
<td>600 mg b.i.d. (12 caps/day)</td>
<td>Yes</td>
<td>$771.54</td>
</tr>
<tr>
<td>Saquinavir soft-gelatin (Fortovase®, Roche)</td>
<td>1,200 mg t.i.d. (18 caps/day)</td>
<td>Yes (unless taken with ritonavir)</td>
<td>$720.96</td>
</tr>
<tr>
<td>Saquinavir hard-gelatin (Invirase®, Roche)*</td>
<td>600 mg t.i.d. (9 caps/day)</td>
<td>No (no food effect when taken with ritonavir)</td>
<td>$699.30</td>
</tr>
</tbody>
</table>

* This drug should not be prescribed without ritonavir boosting. Price does not include ritonavir.

b.i.d. = twice a day; q.d. = once a day; t.i.d. = three times a day.

with HIV-1 infection. Fosamprenavir is a new alternative and offers some advantages over other agents in its class. The dosing flexibility and decreased pill burden associated with its use are clearly advantageous, compared with its predecessor, amprenavir capsules. On the basis of its ADEs and drug–drug interaction profiles, fosamprenavir is comparable to the other PIs currently available.

Preliminary data suggest that the combination of fosamprenavir and ritonavir is equivalent to lopinavir/ritonavir and that the use of fosamprenavir in both HAART-naive and HAART-experienced patients has successfully resulted in reduced HIV-1/RNA levels. Future clinical trials will provide more evidence on the exact role of fosamprenavir therapy in the management of HIV-1 infection.

REFERENCES


