Atazanavir: A Once-Daily Protease Inhibitor for the Treatment of HIV-1 Infection

Marie Vilme, PharmD, Deidree Edwards, PharmD, and Shvawn McPherson-Baker, PharmD, MPH, BCPS

INTRODUCTION

The addition of protease inhibitors (PIs) to antiretroviral regimens has become an effective strategy for decreasing morbidity and mortality related to human immunodeficiency virus (HIV) infection. Although PI-based regimens exhibit potent antiviral activity, challenges faced in selecting an appropriate regimen include pill burden, long-term complications, and resistance.

As a result of their poor bioavailability, the first marketed PIs necessitated a large pill size, an increased pill count, frequent dosing schedules, and food or water restrictions. More recently, “pharmacokinetic boosting” has been used to enhance the usefulness of PIs by coadministration of low-dose ritonavir (Norvir®, Abbott) with other PIs. This advance has allowed for increased drug exposure and prolonged serum half-lives without greatly increasing toxicity. These enhanced regimens include simple dosing schedules, the need for fewer tablets, and limited food restrictions, all resulting in improvement of patients’ adherence to medication regimens.

Despite the improvement in the treatment of HIV and acquired immunodeficiency syndrome (AIDS) with the advent of PIs, concerns have arisen about their use. Metabolic complications associated with PI-based regimens include fat mal-distribution, dyslipidemia, and insulin resistance. Although the underlying HIV process itself is linked with lipid abnormalities, dyslipidemia denotes the metabolic complication that is probably most commonly related to PI use. Lipid changes include elevated levels of total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and triglycerides (TGs). Treatment options include switching from triple antiretroviral therapy with a PI to a non-nucleoside reverse transcriptase inhibitor (NNRTI). An alternative might be to add a lipid-lowering agent to a successful PI-based regimen.

Another challenge in selecting an appropriate PI-based regimen is drug resistance. Although PIs represent the highest genetic barrier to resistance, cross-resistance is limited. As a result, the usefulness of initiating another PI after the development of resistance in one member of the PI drug class is limited. Options for diminishing resistance include pharmacokinetic boosting and the development of PIs that would be less likely to induce or be susceptible to cross-resistance.

Currently, eight PIs are available in the U.S. and have been approved by the Food and Drug Administration (FDA): indinavir sulfate (Crixivan® Merck), saquinavir mesylate (Fortovase®, Roche), nelfinavir (Viracept®, Agouron), ritonavir (Norvir®, Abbott), amprenavir (Agenerase®, GlaxoSmithKline), lopinavir/ritonavir (Kaltra®, Abbott), fosamprenavir (Lexiva®, GlaxoSmithKline), and atazanavir sulfate (Reyataz®, Bristol-Myers Squibb Virology). Atazanavir received FDA approval on June 20, 2003, for the treatment of HIV infection.

Atazanavir should be used in combination with other antiretroviral agents. It is indicated for treatment-naïve and treatment-experienced HIV-positive adults. This new agent is the first drug in its class that allows once-daily dosing. Because of its unique structure, reduced pill burden, and favorable long-term side-effect profile, it may offer some important advantages over the other currently available PIs.

CHEMISTRY AND PHARMACOLOGY

Unlike other PIs, atazanavir sulfate is a derivative of azapeptide analogues of the HIV protease. Its chemical structure is (3S, 8S, 9S, 12S)-3,12-bis(1,1-dimethylthiethyl)-8-hydroxy-11-dioxo-9-(phenylmethyl)-6-[(4-(2-pyridinyl)phenyl)methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). The molecular formula is C_{38}H_{52}N_{6}O_{7}·H_{2}SO_{4}, and the molecular weight is 802.9 (sulfuric acid salt). Figure 1 shows the chemical structure.

Atazanavir is a selective inhibitor of the HIV-1 aspartic protease enzyme. This enzyme is used in the HIV-replication process to cleave viral Gag and Gag-Pol polyproteins, preventing the formation of infectious virons. When tested in combination with different nucleoside reverse transcriptase inhibitors (NRTIs) and PIs, atazanavir produced additive to synergistic antiviral activity.

RESISTANCE PROFILE

Development of resistance to antiretroviral therapy usually results from incomplete virological response. In vitro, amino acid changes in the protease
enzyme on codons, such as N88S, I50L, I84V, A71V, and M46I, have been correlated with atazanavir resistance.\textsuperscript{17} The development of atazanavir resistance depends on the type of HIV-infected cell, the corresponding strain of HIV, drug concentrations, and whether the patient is PI treatment-naive or PI-experienced.\textsuperscript{14} In particular, resistance to atazanavir occurs more frequently in the presence of other PIs that cause resistance.\textsuperscript{19} The profile of resistance for atazanavir is distinct because there is no obvious cross-resistance pattern between atazanavir and other PIs.\textsuperscript{20}

In several studies, PI-naive patients who developed resistance to atazanavir often developed the I50L mutation, with or without the A71V codon change; this change resulted in an increased susceptibility to other PIs.\textsuperscript{13–15,17} In contrast, PI-experienced patients who were switched to atazanavir exhibited mutations in the protease enzyme on the following codons: L10/I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, I84V, and L90M.\textsuperscript{18}

Typically, the presence of at least three mutations conferred resistance to atazanavir and the development of more than five mutations correlated with viral resistance.\textsuperscript{13–18} Codon mutations such as I84V, G48V, L90M, A71V/T, N88S/D, and M46I appear to confer high cross-resistance to atazanavir and other PIs.\textsuperscript{14} These mutations conferred high cross-resistance to many other PIs, such as I84V, G48V, L90M.\textsuperscript{18}

As a result, both amprenavir and lopinavir/ritonavir can serve as atazanavir switching alternatives.\textsuperscript{17} Because ritonavir-boosting regimens appear to exhibit less cross-resistance, this combination is a practical option in PI-experienced patients.\textsuperscript{18}

**PHARMACOKINETICS**

After oral administration of atazanavir 400 mg once daily, taken with a light snack or meal, maximum plasma concentrations ($C_{\text{max}}$) of 2,918 to 5,867 ng/ml are reached in approximately two to four hours.\textsuperscript{13,17,20} Values for the area-under-the-plasma concentration (AUC) time curve during a dosage interval at a steady state range from 18,590 to 33,550 ng $\cdot$ hours/ml.\textsuperscript{13,17,20} The trough ($C_{\text{min}}$) steady-state plasma concentrations range from 149 to 219 ng/ml, exceeding the concentration required to inhibit 50% of HIV-1 replication (EC$_{50}$) for more than 36 hours.\textsuperscript{13,17,20}

Atazanavir is moderately absorbed after oral administration; its mean bioavailability is 68%.\textsuperscript{13} Food can enhance bioavailability and minimize the variability in absorption.\textsuperscript{13,17} Peak concentrations are reached within two hours, and nonlinear pharmacokinetic properties are observed over the dosage range of 200 to 800 mg daily.\textsuperscript{13,17,20}

Atazanavir is bound to albumin by 86% and to alpha$_1$-acid glycoprotein by 89%, and it is extensively metabolized by the hepatic cytochrome P-450 (CYP450) enzyme system.\textsuperscript{13,17} Atazanavir inhibits CYP3A4, CYP2C9, and CYP1A2 isoenzymes and uridine glucuronyltransferase (UGT)1A1.\textsuperscript{13,14,17,18} After a one-time 400-mg dose of C-atazanavir, most of the drug is recovered in the feces and approximately 13% is recovered in the urine.\textsuperscript{13} The mean elimination half-life is seven hours, and the major pathway of elimination is biliary.\textsuperscript{13,16}

During the evaluation of atazanavir in healthy patients, no clinically important pharmacokinetic changes were observed as a result of their age or sex.\textsuperscript{16} The pharmacokinetic data available regarding pediatric patients are insufficient, and no pharmacokinetic data are available about patients with renal insufficiency.\textsuperscript{16,18} Because of the elevated AUC values reported in patients with hepatic impairment (Child-Pugh class B and C) in comparison to healthy patients, increased serum concentrations of atazanavir are expected in patients with moderate-to-severe hepatic impairment.\textsuperscript{13,18} Atazanavir is not recommended for patients with severe hepatic disease.\textsuperscript{13,18}

**CLINICAL TRIALS**

A limited number of trials involving atazanavir have been published. Clinical data from phase 2 and 3 trials led to the FDA’s approval of atazanavir. In various continued on page 31
studies, the efficacy of atazanavir was evaluated in antiretroviral-naive as well as in treatment-experienced patients. A review of these studies follows.

### Antiretroviral-Naive Patients

**The Sanne Study**

Sanne et al. conducted a 48-week trial comparing the efficacy of atazanavir (at three dose ranges) with nelfinavir in combination with didanosine (ddI; Videx®, Bristol-Myers Squibb Immunology) and stavudine (d4T; Zerit®, Bristol-Myers Squibb Immunology) in antiretroviral-naive HIV-infected subjects. The study was divided into two stages.

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Eligible HIV-1 infected patients had to be 18 years of age or older and had to have HIV-1 RNA levels between 5,000...
Table 3  Coadministration of Atazanavir with Agents That May Require Dose Alterations

<table>
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<tr>
<td><strong>Eplerenone</strong></td>
<td>Both eplerenone and atazanavir are substrates of CYP3A4.</td>
<td>Plasma concentration of either or both drugs may increase because of competition for the enzymatic pathway.</td>
<td>Initial dosage should be eplerenone 25 mg daily. Dose adjustment may be necessary when atazanavir is discontinued.</td>
</tr>
<tr>
<td><strong>Antacids</strong></td>
<td>Increased gastric pH from buffer</td>
<td>Decreased atazanavir levels</td>
<td>Separate the administration of atazanavir and antacids to avoid potential interactions; give atazanavir two hours before or one hour after the antacids.</td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td>This agent is a substrate and an inhibitor of CYP3A4.</td>
<td>Atazanavir coadministration increases clarithromycin serum concentrations.</td>
<td>Reduce clarithromycin dose by 50%; monitor for QT prolongation.</td>
</tr>
<tr>
<td><strong>Amiodarone, lidocaine, quinidine</strong></td>
<td>Atazanavir inhibits CYP3A4.</td>
<td>Increased antiarrhythmic blood levels</td>
<td>Avoid systemically administered lidocaine; however, when they are used together, monitor serum lidocaine level. Dose reduction may be indicated.</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Atazanavir competitively inhibits enzymes CYP3A4, CYP1A2, and CYP2C9.</td>
<td>Concentrations of drugs that are substrates of these enzymes may be increased with concomitant atazanavir.</td>
<td>Closely monitor patient’s International Normalized Ratio.</td>
</tr>
<tr>
<td><strong>Rifabutin</strong></td>
<td>—</td>
<td>Coadministration of atazanavir and rifabutin increases the AUC by 250%.</td>
<td>Reduce dose up to 75% (150 mg three times per week or every other day).</td>
</tr>
<tr>
<td><strong>Didanosine, buffered formulation</strong></td>
<td>Increased gastric pH from buffer</td>
<td>Decreased atazanavir levels</td>
<td>Use enteric-coated tablet, or give atazanavir with food two hours before or one hour after didanosine-buffered formulations.</td>
</tr>
<tr>
<td><strong>Efavirenz</strong></td>
<td>This agent is a CYP3A4 inducer.</td>
<td>Decreased atazanavir levels</td>
<td>Boost atazanavir 300 mg with ritonavir 100 mg; coadminister with efavirenz (all as a single dose) with a light meal.</td>
</tr>
<tr>
<td><strong>Saquinavir</strong></td>
<td>This agent is a substrate and an inhibitor of CYP3A4.</td>
<td>Increased concentration of saquinavir</td>
<td>No dosing adjustment required</td>
</tr>
<tr>
<td><strong>Ritonavir</strong></td>
<td>This agent is a substrate and an inhibitor of CYP3A4.</td>
<td>Coadministration of ritonavir with atazanavir results in a higher C&lt;sub&gt;max&lt;/sub&gt; and AUC of atazanavir.</td>
<td>Decrease atazanavir dose to 300 mg when given with 100 mg of ritonavir.</td>
</tr>
<tr>
<td><strong>Tenofovir disoproxil fumarate</strong></td>
<td>Coadministration reduces atazanavir’s AUC concentration.</td>
<td>Interaction may lead to loss or lack of virological response and possible resistance to atazanavir.</td>
<td>Boost atazanavir 300 mg with ritonavir 100 mg.</td>
</tr>
<tr>
<td><strong>Diltiazem, verapamil</strong></td>
<td>These agents are substrates and inhibitors of CYP3A4.</td>
<td>Increased plasma concentration of either atazanavir or the interacting drug. Concurrent atazanavir use has led to a two-fold increase in the AUC of diltiazem.</td>
<td>Consider a 50% dose reduction of diltiazem as well as ECG monitoring.</td>
</tr>
<tr>
<td><strong>Amlodipine, nifedipine, felodipine, nicardipine, nimodipine</strong></td>
<td>These agents are metabolized by CYP3A4; nicardipine is also an inhibitor of CYP3A4.</td>
<td>Decreased blood concentration of these drugs</td>
<td>Monitor patient carefully, especially when dose is titrated.</td>
</tr>
<tr>
<td><strong>Sildenafil</strong></td>
<td>Atazanavir inhibits its metabolism.</td>
<td>May result in increased plasma concentrations of sildenafil; there is an increased risk of hypotension, visual changes, and priapism.</td>
<td>Do not use more than 25 mg of sildenafil in 48 hours with atazanavir.</td>
</tr>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>Atorvastatin is metabolized by CYP3A4.</td>
<td>Atazanavir inhibits atorvastatin metabolism.</td>
<td>Monitor side effects, reduce dose.</td>
</tr>
<tr>
<td><strong>Famotidine, nizatadine, ranitidine, cimetidine</strong></td>
<td>Atazanavir solubility decreases as gastric pH increases.</td>
<td>Because of increased gastric pH, coadministration of these agents is not recommended. Significant reduction in plasma concentrations can occur, which may lead to therapeutic failure and development of resistance.</td>
<td>Avoid coadministration. If a histamine H&lt;sub&gt;2&lt;/sub&gt;-blocker must be used with atazanavir, separate the doses by 12 hours.</td>
</tr>
<tr>
<td><strong>Cyclosporine, sirolimus, tacrolimus</strong></td>
<td>These agents are substrates of CYP3A4; cyclosporine is also an inhibitor of CYP3A4.</td>
<td>Atazanavir may inhibit their metabolism and increase their serum concentration.</td>
<td>Monitor serum concentration levels.</td>
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Table continued on next page
and 750,000 copies/ml (stage 1) or 2,000 or more copies/ml (stage 2), and CD4 cell counts of 100 cells/mm^2 (stage 1) or more, or 75 cells/mm^2 (stage 2) or more 14 days before randomization. Patients also had to be antiretroviral therapy-naive (defined as receiving less than four weeks of NRTI therapy and/or less than one week of NNRTI or PI therapy).

During the first two weeks of the study, patients received atazanavir 200, 400, or 500 mg once daily with nelfinavir 750 mg three times daily as monotherapy. This regimen was followed by the addition of didanosine 400 mg once daily and stavudine 40 mg twice daily for the remaining 46 weeks.

Changes from baseline HIV-1 RNA levels were compared at the 2nd and 48th weeks. At week 2, during monotherapy, mean changes in HIV-1 RNA levels were comparable across treatment groups in stage 1 subjects; in stage 2 subjects, mean changes from baseline were 1.27 log10 copies/ml with atazanavir 200 mg; −1.27 log10 copies/ml with atazanavir 400 mg; −1.58 log10 copies/ml with atazanavir 500 mg; and −1.36 log10 copies/ml with nelfinavir (P < .05 for atazanavir 500 mg vs. nelfinavir).

At week 48, decreases from the baseline in HIV-1 RNA levels were similar across all dosage regimens for patients with stage 2 disease. The proportion of participants in stage 2 with HIV-1 RNA levels below 400 copies/ml as follows: 61% in the atazanavir 200-mg group of patients; 64% in the atazanavir 400-mg group; 59% in the atazanavir 500-mg group; and 56% in the nelfinavir group.

At 48 weeks, increases in CD4 cell counts from baseline values were comparable across the treatment groups: atazanavir 200 mg, 220 cells/mm^3; atazanavir 400 mg, 221 cells/mm^3; atazanavir 500 mg, 208 cells/mm^3; and nelfinavir, 185 cells/mm^3.

### The Murphy Study

In a 48-week phase 2 trial, the efficacy of atazanavir 400 mg or 600 mg once daily was compared with nelfinavir 1,250 mg twice daily. Each dose was combined with didanosine and stavudine in antiretroviral-naïve patients.

To be eligible for enrollment, patients with HIV-1 infection had to be at least 18 years of age, had to be new to antiretroviral therapy, and had to have HIV-1 RNA levels of 2,000 copies/ml or greater and CD4 cell counts of 100 × 10^9 cells/liter or more without a prior AIDS diagnosis.

The primary efficacy endpoint was a mean change in HIV-1 RNA levels from baseline through 48 weeks. Mean changes in HIV-1 RNA (log_{10} copies/ml) at 48 weeks were −2.51 with atazanavir 400 mg, −2.58 with atazanavir 600 mg, and −2.31 with nelfinavir.

Although the overall number of patients reaching HIV-1 RNA levels below 400 copies/ml at 48 weeks was comparable in all of the treatment groups, the intent-to-treat (ITT) population had significantly more patients in the atazanavir 600-mg group (67%) than in the nelfinavir group (53%) who achieved HIV-1 RNA levels below 400 copies/ml (P < .05). At 48 weeks, atazanavir 400 mg and 600 mg and nelfinavir were equally effective in increasing mean CD4 cell counts (234 × 10^9, 243 × 10^9, 211 × 10^9 cells/liter, respectively).

### The Squires Study

In another 48-week trial, investigators compared the efficacy of once-daily atazanavir with once-daily efavirenz, each in combination with fixed-dose zidovudine and lamivudine in treatment-naïve, HIV-positive patients. The primary efficacy assessment was the proportion of treated subjects with HIV-1 RNA levels below 400 copies/ml through 48 weeks. Secondary assessments included changes from baseline through the 48th week in plasma log_{10} HIV-1 RNA values and CD4 cell counts. At week 48, 70% of patients in the atazanavir group achieved HIV-1 RNA levels below 400 copies/ml, compared with 64% of the efavirenz patients.

By week 24, both atazanavir and efavirenz patients achieved mean reductions in HIV-1 RNA levels of approximately 2.7 log_{10} copies/ml. This level was maintained through the 48 weeks. Median CD4 cell counts increased at similar degrees and rates in the treatment groups.

### Treatment-Experienced Patients

#### The Haas Study

Haas et al. conducted a 48-week pilot study to compare the efficacy of once-daily atazanavir/saquinavir with twice-daily ritonavir/saquinavir in antiretroviral-experienced adults. Patients were randomly assigned to receive atazanavir 400 mg/saquinavir 1,200 mg once daily; atazanavir 600 mg/saquinavir 1,200 mg once daily; or ritonavir 400 mg/saquinavir 400 mg twice daily. The study was blinded only in regard to atazanavir and was open label for all of the other drugs. Patients also received two NRTIs to which phenotypic sensitivity was demonstrated.

The efficacy assessments included changes from baseline in HIV-1 RNA levels and CD4 cell counts, and the proportion of patients achieving a virological

### Table 3: Coadministration of Atazanavir with Agents That May Require Dose Alterations (continued)

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<td>Amitriptyline, clomipramine, desipramine, doxepin, nortriptyline</td>
<td>Atazanavir competitively inhibits CYP3A4, CYP1A2, and CYP2C9.</td>
<td>Concentrations of drugs that are substrates of these enzymes may be increased with concomitant atazanavir use.</td>
<td>Monitor patients for anticholinergic effects (e.g., sedation, confusion, and constipation).</td>
</tr>
<tr>
<td>Ethinyl estradiol, norethindrone</td>
<td>Atazanavir inhibits the metabolism of these agents.</td>
<td>Increased ethinyl estradiol and norethindrone levels</td>
<td>Watch for side effects; possible dose reduction.</td>
</tr>
</tbody>
</table>

AUC = area-under-the-curve concentration; Cmax = peak concentration; ECG = electrocardiographic.
ADVERSE DRUG EVENTS

In clinical trials, atazanavir was relatively well tolerated, and ADEs were similar to those reported with comparator antiretroviral agents. In studies comparing atazanavir with nelfinavir, diarrhea occurred more commonly in the nelfinavir-treated patients than in atazanavir-treated patients. Subjects receiving atazanavir reported nausea more frequently than did patients receiving nelfinavir. However, the incidence of jaundice and scleral icterus was reported only in the atazanavir treatment groups.

In the study by Murphy et al., four patients receiving atazanavir 600 mg discontinued therapy as a result of hyperbilirubinemia. In addition, grade 3 to 4 elevations in total bilirubin were dose-related and were observed more often in the atazanavir-treated patients (41% of patients taking the 400-mg dose and 58% taking 600 mg) than in the nelfinavir-treated patients (4%). Additional ADEs comparing atazanavir with nelfinavir therapy are shown in Table 1.

In clinical trials with antiretroviral therapy–naive and treatment-experienced patients, atazanavir was not associated with clinically relevant increases in TC, fasting TG, or LDL-C, compared with results from nelfinavir and ritonavir, respectively. Haas et al. demonstrated that patients in the atazanavir arms had favorable lipid changes and lacked influence on TC, LDL-C, and TG, compared with the ritonavir/saquinavir arm.

At 48 weeks, mean changes in LDL-C levels from baseline for atazanavir 400 mg, atazanavir 600 mg, and ritonavir were –0.6, –6.7, and 23.2%, respectively (P < .05). Mean changes in TG levels, from baseline to 48 weeks, were –4.8 for atazanavir 400 mg, –27.1 for atazanavir 600 mg, and 93% for ritonavir (P < .001).

In the clinical trial by Squires et al. that compared atazanavir with efavirenz, the changes (in percent) for the atazanavir-treated patients in TC, LDL-C, high-density lipoprotein-cholesterol (HDL-C), and TG levels were as follows: +2%, +1%, +13% and –9%, in comparison with efavirenz-treated subjects (+21%, +18%, +24%, +23%, respectively).

Atazanavir treatment did not alter fasting glucose or insulin levels.

**Drug Interactions**

Like many other PIs, atazanavir is a CYP3A4 substrate. This agent competitively inhibits the enzymes of CYP3A, CYP2C9, and uridine glucuronosyltransferase (UGT) 1A1, an enzyme that conjugates bilirubin, causing elevations in unconjugated bilirubin. Atazanavir can induce inhibition of CYP3A4 isoenzymes and increase serum concentration of drugs that are metabolized by this system; therefore, the concurrent use of such agents is contraindicated.

Table 2 presents the medications that are prohibited from being coadministered with atazanavir. These drugs include the ergot alkaloids, hydroxymethylglutaryl–coenzyme A (HMG–CoA) reductase inhibitors (statins), selected benzodiazepines, and calcium-channel blockers.

Rifampin and St. John’s wort should not be used with atazanavir because they induce CYP3A4 and may significantly decrease plasma concentration of all PIs. This can lead to HIV treatment failure and to the development of resistance.

Table 3 presents agents that might require dose alterations when coadministered with atazanavir. The current use of atazanavir and rifabutin (Mycobutin™) increases the rifabutin AUC concentration by 250%, consequently, the dosage of rifabutin must be reduced by 75% (e.g., 150 mg every other day or three times per week).

Immunosuppressants such as cyclosporine, sirolimus, and tacrolimus are substrates of CYP3A4, and atazanavir may inhibit their metabolism, leading to serious ADEs, including prolongation of the QT interval.

Erythromycin and clarithromycin are both inhibitors and substrates of CYP3A4; coadministration with atazanavir may result in increased plasma concentration of either of these drugs. Because increasing plasma concentration of clarithromycin may result in QT prolongation, reducing the dose of clarithromycin by 50% is recommended.

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if antacids, buffered medications, histamine (H2) receptor antagonists, and proton-pump inhibitors are coadministered.

Because atazanavir has the potential to prolong the PR interval on the electrocardiogram (ECG) when used in combination with calcium-channel blockers, ECG monitoring is recommended. Diltiazem (Cardizem®, Biovail) and verapamil (Calan®, Pfizer) are both substrates and inhibitors of CYP3A4, and they can prolong the PR interval. A dose reduction of 50% and ECG monitoring...
are recommended for patients taking di- 
tiazem in combination with atazanavir. 
Caution should also be exercised with 
other calcium-channel blockers that are 
metabolized via CYP3A4, including amo- 
dipine besylate (Norvasc®, Pfizer), 
felodipine (Plendil®, AstraZeneca), 
icardipine (Cardene®, Yamanouchi), 
niludipine (Procardia®, Pfizer), and ni-
modipine (Nimotop®, Bayer).13–18

**DOSEAGE AND ADMINISTRATION**

Atazanavir sulfate is available in 100-, 
150-, and 200-mg capsules.13–18 The re-
commended dose is 400 mg (two 200-mg 
capsules) once a day taken with food.12–18

With efavirenz coadministration, the recommended dosage is atazanavir 300 
mg, ritonavir 100 mg, and efavirenz 600 
mg.12–18

With the coadministration of tenofovir 
disoproxil fumarate (Viread®), the atazanavir dose should be reduced to 
300 mg daily with ritonavir 100 mg.16 
Atazanavir without ritonavir should not 
be given with efavirenz or tenofovir.

Atazanavir taken with didanosine 
buffered formulations should be given 
(with food) two hours before or one hour 
after didanosine administration.13,16

Atazanavir should be used with cau-
tion in patients with mild-to-moderate 
hepatic insufficiency.12–18 A dose re-
duction to 300 mg once daily should be 
considered for patients with moderate 
hepatic insufficiency (Child-Pugh class 
B).12–18 No dosage adjustment is neces-
sary for patients with renal insuffi-
ciency.13

**COST**

At the recommended dose of 400 mg 
once daily, the average wholesale price 
(AWP) for atazanavir is approximately 
$10,000 per year.26 The cost is similar to 
that of other PIs. Approximate prices 
range from $6,000 to $10,000 per year.

**CONCLUSION**

Unlike earlier-generation PIs that have 
been used in the treatment of HIV-1 infec-
tion, atazanavir offers once-daily dosing, 
a minimal impact on lipid parameters, 
and a distinct resistance profile. This aza-
peptide PI moderately inhibits hepatic 
CYP450 enzymes and interacts with se-
veral drugs.

Commonly reported ADEs include 
nausea, elevations in unconjugated bili-
rubin, and jaundice. For antiretroviral-
naive patients, an atazanavir-based regi-
men may be considered an important se-
lection. Clinical trials of atazanavir 
demonstrate the usefulness of this 
agent as the sole PI for treatment-naïve 
patients. When boosted with ritonavir or 
coadministered with saquinavir, ata-
zanavir might be an alternative for 
patients experiencing virological failure 
with other PI-containing regimens.

**REFERENCES**

1. Palella FJ Jr, Delaney KM, Moorman AC, 
et al. Declining morbidity and mortality among 
patients with advanced human immunodeficiency 
virosis infection. HIV Outpatient Study Investigators. 

2. Sax PE. Do new protease inhibitors offer 
modified management options? *J Acquir Immune 

3. Benjamin Y, Markowitz. Do new 
protease inhibitors offer modified effectiveness? 

 inhibitors provide more treatment options. 
*AIDS Patient Care STDs* 2003;17:551– 
564.

5. Panel on Clinical Practices for Treatment of 
HIV Infection, convened by the Depart-
ment of Health and Human Services. 
Guidelines for the use of antiretroviral agents 
in HIV-infected adults and adoles-
 cents (October 2004). Available at: 

6. Acosta EP. Pharmacokinetic enhance-
ment of protease inhibitors. *J AIDS* 2002; 
29:S11–S18.

7. Maye J. Overcoming obstacles to the 
success of protease inhibitors in highly 
active antiretroviral therapy regimens. 
*AIDS Patient Care STDs* 2002;16:585– 
597.

8. Nolan D. Metabolic complications associ-
ed with HIV protease inhibitor therapy. 
*Drugs* 2003;63(23):2555–2574.

9. Mantel-Ten Hove AS, Koosterman JM, 
Maitland-van der Zee AH, et al. Drug-
induced lipid changes: A review of the 
tenanted effects of some commonly 
used drugs on serum lipid levels. *Drug 

10. Martinez E, Garcia-Viioje MA, Blanco JL, 
et al. Impact of switching from human 
immunodeficiency virus type 1 protease 
inhibitors to efavirenz in successfully 
treated adults with lipodystrophy. *Clin 

11. Kozai M. Cross-resistance patterns 
among HIV protease inhibitors. *AIDS 

12. FDA. Available at: www.fda.gov/cder/ 
foi/nda/2003/021567_reyataz_loc.htm.

13. Reyataz® (atazanavir sulfate) package 
insert. Princeton, NJ: Bristol-Myers 
Squibb; June 2003.

aza-peptide inhibitor of HIV-1 protease. 

15. Atazanavir drug monograph. Available 
at: www.rxlist.com/cgi/generic3/
reyataz.htm.

Evaluations; Micromedex Healthcare Series, 
Vol 121. Available at: www.visn8.med.va.
gov.

17. Terriff CM. Atazanavir (Reyataz®): A 
new HIV protease inhibitor. *Adv Pharm-
ery* 2004;2(1):5–11.

18. Musial BL, Chojnacki JK, Coleman CI. 
Atazanavir: A new protease inhibitor to treat HIV infection. *Am J Health Syst 

Distinct cross-resistance profiles of the 
new protease inhibitors amprenavir, 
lopinavir, and atazanavir in panel of 
1261.

*Drugs* 2003;63(16):1679–1693.

with atazanavir plus saquinavir in patients 
falling highly active antiretroviral ther-
apy: A randomized comparative pilot trial. 

of a phase 2 clinical trial at 48 weeks 

23. Murphy RL, Sanne I, Cahn P, et al. Dose-
ranging, randomized, clinical trial of 
atazanavir with lopinavir and stavudine 
in antiretroviral-naïve subjects: 48-week 

Comparison of once-daily atazanavir with 
efavirenz, each in combination with fixed-
dose zidovudine and lamivudine, as ini-
tial therapy for patients infected with HIV. 
*J Acquir Immune Defic Syndr* 2004;36: 
1011–1019.

Long-term efficacy and safety of ata-
zanavir with stavudine and lamivudine in 
patients previously treated with nelfinavir 
or atazanavir. *J Acquir Immune Defic 