Atazanavir: A new protease inhibitor to treat HIV infection

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At the end of 2002, over 816,000 individuals in the United States and 42 million people worldwide were infected with human immunodeficiency virus (HIV). Current guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents state that the primary objectives of antiretroviral therapy are the maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. The advent of HIV-1 protease inhibitors (PIs) and nonnucleoside reverse-transcriptase inhibitors (NNRTIs) has resulted in highly active antiretroviral therapy (HAART) when given in conjunction with two nucleoside reverse-transcriptase inhibitors (NRTIs) and has aided many patients in achieving the aforementioned HIV-related treatment goals.

Despite data supporting the efficacy and safety of PIs, concerns have emerged regarding PI-containing regimens. As with any antiretroviral agent, viral resistance often develops over time, resulting in treatment failure. This is further perpetuated by suboptimal patient adherence due to the high pill burden, increased regimen complexity, and adverse effects (e.g., nausea, vomiting, diarrhea) which are particularly common with PI-containing regimens. As a result, failure rates as high as 50% after only 48 weeks of treatment have been observed in patients taking these regimens. Moreover, PIs are associated...
with the development of unwanted metabolic effects, including hyperglycemia, insulin resistance, and dyslipidemia. In addition, lipodystrophy can result in body habitus changes. These common adverse effects often diminish or prohibit the continued use of PIs. For this reason, HAART regimens containing an NNRTI, such as efavirenz or nevirapine, are increasingly used as an alternative to regimens containing PIs. Intense research has been focused on developing new PIs that lack common metabolic and lipodystrophy adverse effects while maintaining efficacy profiles comparable to other agents in this class.

In June 2003, atazanavir (Reyataz, Bristol-Myers Squibb) received marketing approval from the Food and Drug Administration (FDA) for the treatment of HIV-1 infection in combination with other antiretroviral agents. Atazanavir is added to an antiretroviral armamentarium that now includes seven parent PIs, NRTIs, NNRTIs, nucleotide reverse-transcriptase inhibitors (NRTIs), and fusion inhibitors. This article reviews the available clinical information on atazanavir.

Data sources and selection
Clinical and pharmacokinetic trials of atazanavir were identified through a MEDLINE search (1966-2003). An optimally sensitive search using the medical subject headings (including all subheadings) and text keywords “atazanavir,” “reyataz,” and “BMS-232632” was conducted. The results were then limited to the English language. In addition, studies were identified by retrieving references cited in previously identified studies and review articles. Finally, as atazanavir was recently approved for use in the United States and data were likely available only in abstract form, all available literature citations and pertinent meeting abstracts were obtained from the manufacturer. All articles identified from the data sources were evaluated, and all information deemed relevant was included in this review.

Pharmacology
During the replication process, HIV uses the protease enzyme to cleave the viral protein chains (i.e., gag and gag-pol) into structural proteins and enzymes required for viral replication. Atazanavir is an azapeptide PI that targets the protease enzyme, ultimately resulting in the creation of noninfectious viral particles.

Atazanavir displays antiretroviral activity against laboratory and primary HIV isolates in cell lines and peripheral blood mononuclear cells in the absence of serum proteins (90% effective antiviral concentration = 9-15 nM). This antiretroviral activity is 2- to 20-fold more potent than other available PIs. Atazanavir is highly bound to protein (86%), and, like other PIs, the concentration of nonprotein-bound atazanavir must exceed four times the 50% effective antiviral concentration in order to obtain maximal suppression of viral replication.

In vitro studies have paired atazanavir with a variety of other antiretrovirals commonly used to suppress HIV. Additive or synergistic effects were observed when atazanavir was coadministered with the NRTIs stavudine, lamivudine, didanosine, and zidovudine and the PIs indinavir, nefavir, saquinavir, ritonavir, and amprenavir.

Resistance analysis
Although resistance to antiretrovirals appears to be an inevitable consequence of incomplete HIV suppression, the development of PIs with resistance profiles that are effective against viruses resistant to current treatments is greatly needed. Treatment-naive patients receiving atazanavir commonly develop a protease enzyme mutation on codon 50, which decreases HIV’s susceptibility to atazanavir but may increase its susceptibility to other PIs. However, when atazanavir is given to patients with preexisting PI mutations, the virus’s susceptibility to atazanavir is greatly reduced.

The I50L mutation is the primary resistance mutation that develops in PI-naive patients who do not respond to atazanavir. This key mutation was found in all 19 isolates taken from treatment-naive patients demonstrating virological failure after atazanavir was given as their sole PI for 24-81 weeks. These same isolates retained or had increased susceptibility to the six other PIs evaluated. There was no evidence of decreased susceptibility of amprenavir despite the well-documented relationship between another codon 50 mutation (150V) and amprenavir resistance.

Loss of atazanavir susceptibility has also been correlated with mutations in the protease enzyme on codons L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, V82A/F/S/T, I84V, and L90M. During the replication process, HIV uses the protease enzyme to cleave the viral protein chains (i.e., gag and gag-pol) into structural proteins and enzymes required for viral replication. The I50L mutation is the primary resistance mutation that develops in PI-naive patients who do not respond to atazanavir; the presence of over five mutations has been correlated with reduced sensitivity to atazanavir but may increase its susceptibility in 81.3% of isolates. In 214 viral isolates, which were previously found to be resistant to one or two PIs, 86% of isolates were susceptible to atazanavir, while 96%, 89%, 98%, 26%, 65%, and 91% were susceptible to amprenavir, indinavir, nefavir, ritonavir, and ampranavir, respectively. However, when isolates from the same 214 set that were resistant to three or four PIs were evaluated, only 25% of isolates were susceptible to atazanavir, while 61%, 11%, 42%, 8%, 1%, and 49% were susceptible to amprenavir, indinavir, lopinavir, nefavir, ritonavir, and saquinavir, respectively.
In another evaluation, 40% of patients who had previously taken a PI also had a reduced susceptibility to atazanavir.\textsuperscript{15} Of those same patients, only 18% and 12.5% had a decreased susceptibility to amprenavir and lopinavir–ritonavir, respectively. Moreover, when isolates with a more than 3.5-fold decrease in susceptibility to atazanavir were tested for susceptibility to other PIs, atazanavir demonstrated high levels of cross-resistance with 78%, 85%, 81%, and 84% of nefavir, ritonavir, saquinavir, and indinavir-resistant isolates. Lopinavir–ritonavir demonstrated less cross-resistance to these same isolates, lending support to ritonavir-boosting regimens (which have also been studied with atazanavir) as a viable option in PI-experienced patients.

Pharmacokinetics

The pharmacokinetics of atazanavir have been studied in healthy volunteers and HIV-infected patients.\textsuperscript{9,16,17} Atazanavir exhibits non-linear pharmacokinetics with greater than proportional increases in the area under the concentration–time curve (AUC) and maximum plasma concentration (C\textsubscript{max}) with dosages of 200–800 mg/day.\textsuperscript{9} Administration of atazanavir with a light meal was found to increase the AUC by 70% and C\textsubscript{max} by 57% and reduced pharmacokinetic variability by approximately 50%.\textsuperscript{17} The mean ± S.D. C\textsubscript{max} ranges from 5358 ± 1371 ng/mL to 3152 ± 2231 ng/mL, and the time to maximum concentration (t\textsubscript{max}) is 2.5 hours in healthy volunteers and 2.0 hours in HIV-infected patients receiving 400 mg of atazanavir daily with food. The mean ± S.D. AUC and mean ± S.D. elimination half-life (t\textsubscript{e}) ranges from 29,303 ± 8,263 hr × ng/mL to 22,262 ± 20,159 hr × ng/mL and from 7.9 ± 2.9 hours to 6.5 ± 2.6 hours in healthy volunteers and HIV-infected patients, respectively. Atazanavir is metabolized mainly by the cytochrome P-450 3A4 pathway.\textsuperscript{9,16,17}

Clinical trials

Data on atazanavir is limited to several phase II clinical trials and phase III trials, one of which is still ongoing (Tables 1 and 2).\textsuperscript{18-24} The majority of data are either published in abstract form or available in the new drug application submitted to FDA for review.\textsuperscript{25} The trials used the reductions in HIV RNA and percentage of patients reaching undetectable HIV RNA levels (<400 and <50 copies/mL) as primary endpoints. Historically, viral load reduction has been indicative of decreased morbidity and mortality in HIV-infected patients.\textsuperscript{4} Consequently, FDA recognizes this measurement as a suitable surrogate endpoint in antiretroviral studies.\textsuperscript{26} The secondary efficacy endpoint includes mean changes in CD4+ lymphocyte counts. While CD4+ lymphocyte counts are usually related to the degree of viral load suppression, a favorable CD4+ lymphocyte response can occur with incomplete viral load suppression and may not indicate an unfavorable prognosis. The durability of the immunologic responses that occur with suboptimal suppression of viremia is unknown; therefore, although viral load is the strongest single predictor of long-term clinical outcome, clinicians should also consider sustained rises in CD4+ lymphocyte counts and partial immune restoration as predictors of outcome.\textsuperscript{26}

Phase II trials. The first trial, AI424-007, was a multinational, 48-week, randomized, blinded study comparing the safety, tolerability, and antiretroviral effect of three doses of atazanavir with nefavir in 420 treatment-naive patients.\textsuperscript{18} Eligible patients were age 18 years or older, had less than four weeks of NRTI therapy, had less than one week of NNRTI or PI therapy, and had no HIV-related opportunistic infections. Patients first received either atazanavir 200, 400, or 500 mg once daily or nefavir 750 mg three times daily as monotherapy (for the first 2 weeks) and then in conjunction with stavudine 40 mg twice daily and didanosine 400 mg daily for a total of 48 weeks of treatment. During the 2 weeks of monotherapy, patients exhibited similar reductions in HIV RNA levels (<1.5 log\textsubscript{10} copies/mL), regardless of treatment assignment (p > 0.05 for all comparisons). At the end of 48 weeks, reductions in HIV RNA levels, the number of patients reaching undetectable viral loads (<400 and <50 copies/mL), and increases in CD4+ lymphocyte counts were similar among groups (p values not reported).

A second phase II trial also compared atazanavir with nefavir in 467 treatment-naive patients.\textsuperscript{19} AI424-008 was a randomized, blinded study designed to assess the safety, tolerability, and antiretroviral efficacy of two doses of atazanavir (400 and 600 mg once daily) and nefavir 1250 mg twice daily in combination with lamivudine and stavudine. Subjects were considered eligible if they had a viral load of >2000 copies/mL and a CD4+ cell count of >100 cells/mm\textsuperscript{3}. As in AI424-007, there were no significant differences in the degree of HIV RNA suppression and the number of patients reaching undetectable viral loads among the three treatment groups.

In a follow-up study (AI424-044), patients from AI424-008 with HIV RNA levels of <10,000 copies/mL were followed until week 108 to assess atazanavir’s long-term efficacy.\textsuperscript{20} For the additional weeks of follow-up, both atazanavir treatment groups continued their therapy, and the nefavir group switched to atazanavir 400 mg daily. Responses in HIV RNA levels were similar across all treatment groups in trial AI424-044. At week 108, 76%, 69%, and 75% of patients receiving atazanavir 400 or 600 mg or switched from nefavir, respectively, had viral loads of <400 copies/mL and 47%, 51%, and 49% had viral loads of <50 copies/mL.
CLINICAL REVIEW Atazanavir

Trial AI424-009 evaluated the safety and tolerability of atazanavir 400 and 600 mg once daily compared with ritonavir 400 mg twice daily in 85 antiretroviral-experienced patients (not responding to at least one HAART regimen). Subjects with a viral load of ≥1000 copies/mL and a CD4+ cell count of at least 100 × 10^6 cells/L while on a regimen including a PI or an NNRTI for at least 24 weeks were eligible for the study. Virological response to a previous regimen was also required. Subjects randomized to the atazanavir groups received saquinavir at a dose of 1200 mg once daily while those on ritonavir received saquinavir 400 mg twice a day. The 1200-mg daily dosage of saquinavir administered with atazanavir was chosen on the basis of a previous pharmacokinetic evaluation in which saquinavir’s AUC was found to increase by more than fourfold when concurrently administered with atazanavir. Subjects also received two NRTIs for which phenotypic sensitivity was demonstrated. Phenotypic testing measures a virus’s ability to grow in varying antiretroviral drug concentrations and has been associated with improved viral suppression when used as an aid in the selection of a patient’s antiretroviral regimen. At week 48 the percentage of patients with undetectable viral loads (<400 copies/mL) was similar among groups.

Phase III trials. Trial AI424-034, a double-blind (double-dummy), randomized, multinational, active-controlled phase III study, compared the safety and efficacy of atazanavir 400 mg daily with efavirenz 600 mg daily in 810 treatment-naive adults. Both groups were also given open-label, fixed dosages of zidovudine (300 mg twice daily) and lamivudine (150 mg twice daily). Patients had to be at least 16 years old, have a viral load of ≥2000 copies/mL and a CD4+ cell count of ≥100 cells/mm^3 (≥75 cells/mm^3 if no prior AIDS-defining diagnosis). Results showed...
comparable efficacy in antiretroviral activity between the atazanavir- and efavirenz-treated groups at 48 weeks. Concern has been raised regarding the low percentage of patients responding (<50 copies/mL) to efavirenz in this evaluation compared with prior evaluations of efavirenz. A stricter definition of treatment failure (two viral load measures of >50 copies/mL, even if the viral load was less than 50 copies/mL at week 48) and the type of viral load assay used in this evaluation may explain the lower response rate observed.

AI424-034, an ongoing, open-label, multinational, randomized study, compared the antiretroviral efficacy and safety of atazanavir 400 mg once daily with lopinavir 400 mg plus ritonavir 100 mg twice daily in treatment-naive patients. Atazanavir was also compared with lopinavir 400 mg plus ritonavir 100 mg twice daily in treatment-experienced patients who had not responded to at least one prior HAART regimen including a PI. Of the 229 patients in the study, the mean time of prior treatment was 140 weeks with PIs, 180 weeks with NRTIs, and 85 weeks with NNRTIs. Twenty-four-week results showed that both atazanavir and lopinavir–ritonavir were effective in reducing HIV RNA levels. However, a significantly higher percentage of patients in the atazanavir group achieved virological suppression (<400 and <50 copies/mL) compared with the lopinavir–ritonavir group. Subjects also received two NRTIs for which phenotypic sensitivity was demonstrated. The combinations allowed were (1) zidovudine and lamivudine, (2) stavudine and lamivudine, (3) didanosine and stavudine, (4) zidovudine and lamivudine, (5) zidovudine and didanosine, and (6) abacavir and an appropriate NRTI (didanosine, stavudine, or lamivudine). The mean change from baseline in CD4+ cell count was 176 cells/mm³ in the atazanavir group and 160 cells/mm³ in the lopinavir–ritonavir group.

Table 2.

Phase III Trials of Atazanavir

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline Viral Load and CD4+ Cell Count</th>
<th>Regimen</th>
<th>Mean Change from Baseline in HIV RNA (log_{10} copies/mL)</th>
<th>% Patients with HIV RNA of &lt;400 copies/mL</th>
<th>% Patients with HIV RNA of &lt;50 copies/mL</th>
<th>Mean Change from Baseline in CD4+ Cell Count (cells/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI424-034</td>
<td>4.8 log_{10} copies/mL, 321 cells/mm³</td>
<td>ATV 400 mg q.d. + AZT–3TC (n = 404)</td>
<td>NA</td>
<td>70</td>
<td>32</td>
<td>176</td>
</tr>
<tr>
<td>AI424-043</td>
<td>4.17 log_{10} copies/mL, 318 cells/mm³</td>
<td>ATV 400 mg q.d. + AZT–3TC (n = 401)</td>
<td>NA</td>
<td>64</td>
<td>37</td>
<td>160</td>
</tr>
<tr>
<td>AI424-045</td>
<td>4.45 log_{10} copies/mL, 297 cells/mm³</td>
<td>ATV 300 mg + RTV 100 mg q.d. + TNF + NRTI (n = 120)</td>
<td>−1.86f</td>
<td>64f</td>
<td>39f</td>
<td>83f</td>
</tr>
<tr>
<td>AI424-034</td>
<td>4.8 log_{10} copies/mL, 321 cells/mm³</td>
<td>ATV 400 mg q.d. + AZT–3TC (n = 404)</td>
<td>NA</td>
<td>64</td>
<td>37</td>
<td>160</td>
</tr>
<tr>
<td>AI424-043</td>
<td>4.17 log_{10} copies/mL, 318 cells/mm³</td>
<td>ATV 400 mg q.d. + AZT–3TC (n = 401)</td>
<td>NA</td>
<td>64</td>
<td>37</td>
<td>160</td>
</tr>
<tr>
<td>AI424-045</td>
<td>4.45 log_{10} copies/mL, 297 cells/mm³</td>
<td>ATV 300 mg + RTV 100 mg q.d. + TNF + NRTI (n = 120)</td>
<td>−1.86f</td>
<td>64f</td>
<td>39f</td>
<td>83f</td>
</tr>
</tbody>
</table>

aRandomized, controlled studies; data reported from intention-to-treat analyses. ATV = atazanavir, AZT = zidovudine, 3TC = lamivudine, EFV = efavirenz, OBT = optimized background therapy of two nucleoside reverse transcriptase inhibitors (NRTIs) chosen on the basis of phenotypic testing, LPV = lopinavir, RTV = ritonavir, TNF = tenofovir.

bResults at 48 weeks after randomization in treatment-naive patients.

cResults at 24 weeks after randomization in treatment-experienced patients (not responding to at least one highly active antiretroviral therapy [HAART] regimen).

d<p < 0.05 for comparison of ATV and LPV–RTV.

eResults at 24 weeks after randomization in highly treatment-experienced patients (not responding to at least two HAART regimens consisting of antiretroviral agents from each of the three main classes).

f<p < 0.05 for comparison of ATV–RTV and LPV–RTV.

176 160 94 121 83f 59 90f
study of 347 patients, was designed to assess the efficacy and tolerability of atazanavir 300 mg plus ritonavir 100 mg daily and atazanavir 400 mg plus saquinavir 1200 mg daily compared with lopinavir 400 mg plus ritonavir 100 mg twice daily. Patients were included if they were at least 18 years old and did not respond to at least two HAART regimens that consisted of antiretrovirals from each of the three main classes. Tenofovir and an NRTI were added to all treatment groups at week 2. The mean exposure to a PI, an NRTI, and an NNRTI was 138, 280, and 85 weeks, respectively. The study was designed to examine if the addition of saquinavir, which has a different resistance profile than that of atazanavir, or ritonavir, which interacts to increase serum atazanavir levels, would increase antiretroviral efficacy versus lopinavir-ritonavir. Twenty-four-week data showed comparable antiretroviral activity between the atazanavir-ritonavir and lopinavir-ritonavir treatment groups, which was superior to that of atazanavir-saquinavir (p < 0.05).

Pending trials. The Pediatrics AIDS Clinical Trial Group study 1002-A is an ongoing, 96-week, phase I/II, open-label, pharmacokinetic, and safety trial investigating the use of atazanavir in treatment-naive and experienced pediatric patients. The purpose of the study is to find a safe and tolerable dose of atazanavir in combination with other antiretrovirals for the treatment of HIV-infected patients age three months to 22 years. The study is stratified by age and atazanavir formulation (capsule or powder). Two NRTIs will be used in addition to atazanavir.

Safety and tolerability
During clinical trials, the overall number of adverse events with atazanavir was similar to that found with comparator antiretroviral agents. As many as 68% of patients reported the occurrence of an adverse event while receiving atazanavir 400 mg for up to 108 weeks. The most common adverse effects reported were nausea (14%), headache (6%), rash (6%), and jaundice (5%).

Hyperbilirubinemia with or without jaundice has been reported during clinical trials of atazanavir. Atazanavir inhibits the enzyme responsible for bilirubin conjugation, uridine diphosphate-glucuronosyl transferase 1A1 (UGT 1A1). Most elevations in total bilirubin levels were benign and most commonly occurred within the first week of treatment. In addition, elevations were dosage related, reversible on discontinuation or interruption of drug therapy, and not associated with elevations in transaminase levels. In clinical trials, as few as 1% and as many as one third of patients receiving atazanavir discontinued treatment because of jaundice. Atazanavir’s ritonavir-boosting effect and the occurrence of hyperbilirubinemia need further evaluation; however, data from study AI424-045 have shown that the frequency of jaundice did not appear to increase with ritonavir-boosted atazanavir regimens.

Cardiac effects were observed in the electrocardiograms of healthy volunteers receiving atazanavir. Prolongation of the PR interval by 24 ± 15 ms was seen in patients taking 400 mg of atazanavir; however, these changes did not cause patients to exhibit any symptoms. No significant change in QTc interval was observed in healthy volunteers or HIV-infected patients.

The occurrence of lipoatrophy has been a major concern with previous PIs available in the United States. Evidence from clinical trials of atazanavir indicates that it does not disrupt lipids to the same extent as other PIs or efavirenz. In study AI424-007, 400 mg of atazanavir led to a lower mean increase in total cholesterol than nelfinavir at 48 weeks (6.8% versus 27.8%, respectively) (p < 0.0001). In addition, atazanavir led to lower mean increases in fasting low-density-lipoprotein (LDL) cholesterol levels compared with nelfinavir (p < 0.001). Similar results were observed in study AI424-008.

When compared with the PI combination of lopinavir-ritonavir, atazanavir demonstrated more favorable lipid effects. Total cholesterol levels decreased by 2% in the atazanavir group, while the lopinavir-ritonavir group had a 17% increase (p < 0.0001). Atazanavir showed no deleterious effects on LDL cholesterol and triglyceride levels. Patients in the atazanavir group had a 6% reduction in LDL cholesterol levels and a 2% reduction in triglyceride levels. Patients receiving lopinavir-ritonavir had a 5% increase in LDL cholesterol levels and a 55% increase in triglyceride values (p < 0.05). Both groups increased their high-density-lipoprotein (HDL) cholesterol levels, with a 12% increase in the atazanavir group and 18% in the lopinavir-ritonavir group.

Additional evidence of atazanavir’s favorable lipid effects was demonstrated in AI424-045, even when it was used in combination with another PI (saquinavir or ritonavir). Total cholesterol levels decreased by a mean of 8% and 9% in the atazanavir-ritonavir and atazanavir-saquinavir groups, respectively, and a 3% increase was observed in the lopinavir-ritonavir group (p < 0.0001). Triglyceride levels increased by 31% in the lopinavir-ritonavir group and decreased by 2% and 14% in the atazanavir-ritonavir and atazanavir-saquinavir groups, respectively (p < 0.0001).

Atazanavir’s effect on lipids was compared with that of efavirenz, a drug commonly used as a first-line antiretroviral agent to spare patients from the adverse effects of a PI. Increases in total cholesterol, fasting LDL cholesterol, and fasting triglyceride levels were lower in atazanavir-
treated patients compared with those receiving efavirenz. Mean changes at 48 weeks between atazanavir and efavirenz were 2% and 21%, respectively, for total cholesterol, 1% and 18%, respectively, for LDL cholesterol, and -9% and 23%, respectively, for triglyceride levels (p < 0.0001 for all comparisons).

Drug interactions

Atazanavir inhibits UGT1A1, CYP 1A2 and 2C9 isoenzymes and is both a moderate inhibitor and substrate of the CYP 3A4 isoenzyme. Consequently, interactions between drugs that either inhibit or induce these enzymes should be anticipated. Potential drug interactions that have been evaluated are listed in Table 3.

Atazanavir can significantly increase the serum concentrations of diltiazem, clarithromycin, and rifabutin. The dosage of diltiazem and clarithromycin should be reduced by 50% when they are coadministered with atazanavir. The dosage of rifabutin should be decreased from 300 mg daily to 150 mg three times a week. No dosage adjustments are needed when atazanavir is used in combination with ethinyl estradiol plus norethindrone or atenolol.

While not formally evaluated, because of atazanavir’s effect on the CYP 3A4 isoenzyme system, atazanavir may affect the serum concentration of antiarrhythmic agents (amiodarone, lidocaine, and quinidine), warfarin, tricyclic antidepressants, sildenafil, hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (lovastatin, simvastatin, and atorvastatin), benzodiazepines (midazolam and triazolam), ergot derivatives, cisapride, and the neuroleptic agent pimozide. Coadministration of atazanavir with these agents should be avoided whenever possible; if coadministration is necessary, caution and increased therapeutic drug monitoring should be exercised. In addition, the antimycobacterial agent rifampin and St. John’s wort should not be taken concurrently with atazanavir since they may cause decreased serum concentrations of atazanavir.

Since atazanavir requires an acidic environment for optimal absorption, coadministration of atazanavir and medications that can increase the pH of the stomach (histamine H₂-receptor antagonists and proton-pump inhibitors), as well as the buffered formulation of didanosine can decrease serum atazanavir levels. Consequently, when prescribed together, atazanavir should be taken at least 2 hours before or 1 hour after an antacid or didanosine and 12 hours apart from an H₂-receptor antagonist.

Atazanavir has been evaluated for drug–drug interactions with other antiretroviral agents. When efavirenz was added to atazanavir therapy, the C max and AUC of atazanavir were increased by 41% and 26%, respectively. When atazanavir is administered with 100 mg of ritonavir, the C max and AUC of atazanavir increase by 1.86- and 3.38-fold, respectively. Saquinavir’s C max and AUC increase when coadministered with atazanavir. These interactions may be beneficial to the patient, since they allow for better dosing schedules. For example, patients can be treated with lower doses of atazanavir when this

Table 3.

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Effect on Atazanavir</th>
<th>% Increase or Decrease</th>
<th>Effect on Coadministered Drug</th>
<th>% Increase or Decrease</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>C max</td>
<td>AUC</td>
<td>↔</td>
<td>C max</td>
</tr>
<tr>
<td>Atenolol29</td>
<td>6</td>
<td>28</td>
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<td>Clarithromycin29</td>
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<tr>
<td>Didanosine (buffered) plus stavudine17</td>
<td>89</td>
<td>87</td>
<td>8b</td>
<td>↔</td>
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<td>Diltiazem29</td>
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<td>98</td>
<td>125</td>
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<td>Efavirenz30</td>
<td>14</td>
<td>39</td>
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<tr>
<td>Efavirenz plus ritonavir31,32</td>
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<td>NA</td>
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<td>Ritonavir35</td>
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<td>Ethinyl estradiol plus norethindrone31</td>
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<td>Lamivudine plus zidovudine36</td>
<td>NA</td>
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<td>4f</td>
<td>3f</td>
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</tbody>
</table>

*Caution is recommended.

fEffect not statistically significant.

aEffect on didanosine.

bEffect on stavudine.

cEffect on lamivudine.

dEffect on ethinyl estradiol.

eEffect on norethindrone.

fEffect on lamivudine.

gEffect on zidovudine.
agent is used in conjunction with ritonavir or efavirenz. This in turn may lead to fewer adverse effects. The frequency of saquinavir administration can be decreased from three times daily to once daily when it is used in combination with atazanavir, which can lead to improved patient compliance.

Tenofor may potentially cause a decrease in atazanavir and ritonavir levels; however, the mechanism of this interaction has not been fully elucidated. Dosage and administration

Atazanavir is available as 100-, 150-, and 200-mg capsules. The FDA approved dosage is 400 mg once daily. Other dosing regimens studied include atazanavir 300 mg plus ritonavir 100 mg daily and atazanavir 400 mg plus saquinavir 1200 mg daily. Regardless of the regimen used, atazanavir should be taken with a light meal to increase absorption.

Currently, there is no recommended dosage of atazanavir for the pediatric population; however, a study to identify the most effective and safe dosage of atazanavir in children is currently underway. Atazanavir should be used with caution in patients with mild-to-moderate hepatic insufficiency and is contraindicated in patients with severe hepatic insufficiency. When using atazanavir in patients with mild-to-moderate hepatic insufficiency the dosage should be reduced to 300 mg daily. No dosage adjustment is recommended in renally impaired patients.

Cost

The average wholesale price of a year's supply of atazanavir 400 mg daily is $9698. This cost is similar to that of other PIs (range, $6396-$9240/year's supply).

Formulary considerations

The Department of Health and Human Services, as part of its current HIV treatment guidelines, states that it is imperative that all formularies allow for all FDA-approved antiretroviral options in order to permit maximally individualized therapy. Phase II and III clinical trials of atazanavir have been conducted in treatment-naive, treatment-experienced (not responding to at least one HAART regimen), and highly treatment-experienced patients (not responding to at least two HAART regimens consisting of antiretroviral agents from each of the three main classes). Atazanavir has shown comparable efficacy with other PIs and efavirenz in reducing HIV RNA levels, increasing CD4+ cell counts, and increasing the percentage of subjects reaching clinically detectable HIV RNA levels when given in a sole PI-based regimen in treatment-naive patients, in combination with saquinavir (with phenotypic selection of two NRTIs), in treatment-experienced patients, and as a ritonavir-boosting regimen in highly treatment-experienced patients.

Although antiretroviral resistance appears to be an inevitable consequence of incomplete HIV suppression, the development of new PIs and efavirenz in reducing HIV RNA levels, increasing CD4+ cell counts, and increasing the percentage of subjects reaching clinically detectable HIV RNA levels when given in a sole PI-based regimen in treatment-naive patients, in combination with saquinavir (with phenotypic selection of two NRTIs), in treatment-experienced patients, and as a ritonavir-boosting regimen in highly treatment-experienced patients.

Although antiretroviral resistance appears to be an inevitable consequence of incomplete HIV suppression, the development of new PIs with unique resistance profiles that are effective against virus resistant to current treatments is greatly needed. Treatment-naive patients receiving atazanavir commonly develop a unique protease enzyme mutation at codon 50, which decreases HIV's susceptibility to atazanavir but may increase the susceptibility of the virus to other PIs. When atazanavir is given to patients with preexisting PI mutations, the virus's susceptibility to atazanavir is greatly reduced. In highly treatment-experienced patients, ritonavir-boosting regimens of atazanavir had comparable antiretroviral activity to lopinavir-ritonavir, making it a reasonable choice for salvage therapy.

Failure rates of HAART regimens containing a PI have exceeded 50% at 48 weeks. This high rate of failure can be partially explained by poor patient adherence to PI regimens, which are usually taken multiple times each day and have a high pill burden. Atazanavir is a PI that can be administered once daily. Whether atazanavir's ease of administration will result in increased patient adherence and ultimately improve patients' clinical outcomes has yet to be evaluated.

The frequency and number of adverse events associated with atazanavir appear to be similar to those of other PIs, except for an increased occurrence of hyperbilirubinemia and a decrease in lipid abnormalities with atazanavir. The hyperbilirubinemia associated with atazanavir is dosage related, is benign, is not associated with elevations in other liver function tests, occurs most commonly within the first week of treatment, and is reversible on discontinuation or interruption of the drug therapy. No data on the effect of persistently elevated total bilirubin levels (over five times the upper limit of normal) are available. Atazanavir 400 mg once daily, given in combination with other antiretroviral agents, was selected based on its efficacy and a lower occurrence of hyperbilirubinemia. Alternative antiretroviral therapy may be considered for patients experiencing hyperbilirubinemia; however, dosage adjustments of atazanavir are not recommended since long-term evaluations of lower dose regimens have not been conducted.

The occurrence of lipid abnormalities (elevations in total cholesterol, LDL cholesterol, and triglycerides) which has been a major concern with previous PIs, as well as efavirenz, has not been shown to be troublesome in patients receiving atazanavir in phase II and III trials, even when used in combination with saquinavir or ritonavir. As the survival of HIV-infected patients increases because of improved
HAART, the effect of these lipid abnormalities will become of increasing concern.\textsuperscript{18} In addition, available PIs are commonly potent inhibitors of the CYP isoenzyme system.\textsuperscript{9,25} Consequently, PIs are often associated with drug interactions with medications commonly used to treat hyperlipidemia such as HMG-CoA reductase inhibitors, particularly simvastatin and lovastatin.\textsuperscript{2,40}

Based on atazanavir's efficacy when compared with other PIs and efavirenz,\textsuperscript{18-20,22} its lack of negative lipid effects,\textsuperscript{18-24} its decreased pill burden, and the fact that the resistance mutations associated with atazanavir in PI treatment-naïve patients is associated with improved susceptibility to other PIs,\textsuperscript{13} atazanavir (as the sole PI at a dosage of 400 mg daily) may be most beneficial in PI-naive patients. In treatment-experienced patients, the cross-resistance with other PIs may limit atazanavir's use as the sole PI, as demonstrated by its inferiority to lopinavir–ritonavir during clinical trials.\textsuperscript{15,23} In treatment-experienced patients, atazanavir–saquinavir and atazanavir–ritonavir have been shown to be efficacious.\textsuperscript{21,24} In highly treatment-experienced patients, ritonavir-boosting atazanavir may be used as salvage therapy.\textsuperscript{24}

Conclusion

Atazanavir may be used as a first-line PI, with saquinavir in treatment-experienced patients, or in combination with ritonavir in highly treatment-experienced patients as part of a salvage regimen.

References


