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Atazanavir

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Contents

Abstract

▲ Atazanavir is a novel azapeptide protease inhibitor with high specificity for, and activity against, HIV-1 protease.

▲ The resistance profile of atazanavir is distinct, with an I50L protease substitution appearing to be the signature mutation.

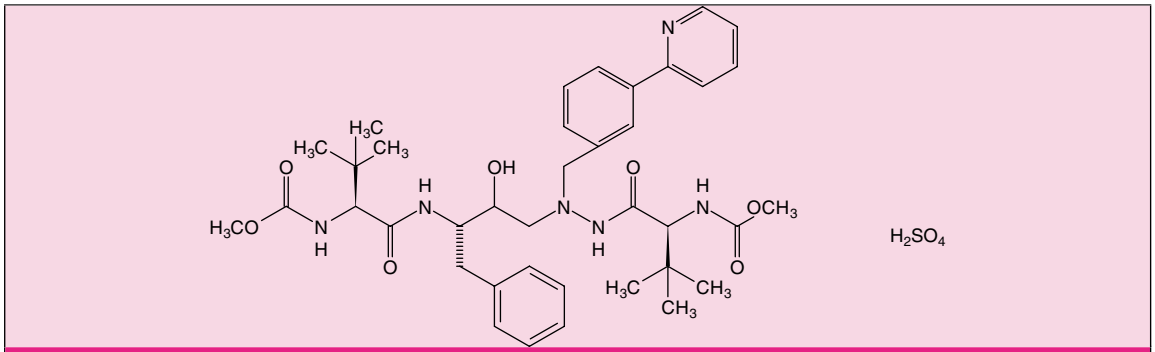
▲ Atazanavir was not associated with increases in total cholesterol, low density lipoprotein-cholesterol or triglyceride levels after 108 weeks.

▲ Atazanavir has a pharmacokinetic profile that allows for once-daily oral administration. It is a moderate inhibitor of hepatic cytochrome P450 enzymes and interacts with several drugs.

▲ In combination with stavudine plus didanosine, atazanavir 200, 400 or 500mg once daily produced a rapid and sustained reduction from baseline in viral load of 2.57, 2.42 and 2.53 $\log_{10}$ copies/mL, respectively, in treatment-naive patients after 48 weeks, compared with a decrease of 2.33 $\log_{10}$ copies/mL with nelfinavir 750mg three times daily.

▲ Nausea was the most clinically relevant adverse event reported in patients receiving atazanavir-based regimens.

Features and properties of atazanavir (BMS-232632, Reyataz™)	
Indication	
HIV infection	In combination with other antiretroviral agents
Mechanism of action	
Antiviral	HIV-1 protease inhibitor
Dosage and administration	
Recommended dose	400mg (two 200mg capsules)
Route of administration	Oral
Frequency of administration	Once daily (with food)
Steady-state pharmacokinetic profile of atazanavir 400mg once daily for 6–14 days in healthy volunteers	
Bioavailability	≈68%
Peak plasma concentration	2918–5867 ng/mL
Time to peak plasma concentration	2–4h
Trough plasma concentration	149–219 ng/mL
Area under the plasma concentration-time curve	18 590–33 500 ng • h/L
Plasma half-life (mean)	5.28h
Adverse effects	
Most frequent	Nausea, elevations in unconjugated bilirubin



Current recommendations for first-line therapy in patients with HIV infection include combinations of a sole (or boosted) protease inhibitor (PI) together with a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone among the options for highly active antiretroviral therapy (HAART).[1-3]

Such triple therapy, while producing durable suppression of viral replication (a measure of a regimen's success is achieving a viral load of <50 HIV RNA copies/mL within 6–9 months of starting treatment[3]), has been associated with the emergence of metabolic, tolerability, adherence, resistance and drug interaction concerns, particularly with PI-based regimens.[4,5]

Long-term complications with PIs, such as dyslipidaemia, are noted as a factor in at least one guideline[3] advocating the use of protease-sparing combinations of two NRTIs with one non-nucleoside reverse transcriptase inhibitor (NNRTI) as first-line therapy.

New drugs are more likely to find a place in the management of HIV infection if they have high bioavailability, a distinct resistance profile, greater potency, fewer adverse effects and a lower rate of long-term complications. Atazanavir (BMS-232632, Reyataz™[1]) is a new azapeptide PI with a pharmacokinetic profile that allows once-daily oral administration.

This review provides a summary of currently available information on the pharmacology and clinical profile of atazanavir in patients with HIV infection.

1. Pharmacodynamic Profile

In Vitro Activity

- Atazanavir differs from the peptidomimetic PIs (e.g. saquinavir, nelfinavir) by its C-2 symmetric chemical structure[6] and was designed and synthesised based on X-ray studies of an enzyme-azadipeptide complex.[7] Like other PIs, it is a highly selective and effective inhibitor of the HIV-1 protease enzyme, blocking the cleavage of viral *gag* and *gag-pol* precursor polyproteins into viral structural proteins, reverse transcriptase, integrase and protease, which results in the release of noninfectious and immature viral particles from cells infected by HIV-1.[8]
- Atazanavir was generally more potent than other PIs against a variety of strains of HIV-1 with a 50% effective concentration (inhibition of 50% of viral replication; EC_{50}) ranging from 2.6 to 5.3 nmol/L

1 Use of tradename is for product identification purposes only and does not imply endorsement.

and an EC_{90} ranging from 9 to 15 nmol/L in cell cultures.[8] The inhibitory quotient (EC_{50} divided by minimum plasma concentration, [C_{min}]) ranged from 10.2 to 25.5, also among the highest reported for PIs without pharmacological boosting.[9,10]

- The presence of 40% human serum (instead of fetal calf serum) increased atazanavir EC_{50} by 2.7- to 3.6-fold (similar to amprenavir, indinavir, ritonavir and saquinavir) in contrast to a 10.8-fold increase in EC_{50} for nelfinavir. A similar effect was observed with the addition of α_1-acid glycoprotein in place of 40% human serum.[8] The combination of growth medium, α_1-acid glycoprotein (1.5 mg/mL) and albumin (4 mg/dL) increased the EC_{50} of atazanavir by 13.4-fold in hollow-fibre unit experiments.[11]
- In two-drug combination studies, atazanavir was additive with all other PIs and NRTIs tested, with the exception of zidovudine, where a weakly synergistic antiviral effect was observed.[8] No antagonistic antiviral or enhanced cytotoxic effects occurred with any combination of atazanavir and an NRTI or another PI.[8] Cytotoxicity with atazanavir alone was seen at concentrations 6500- to 23 000-fold higher than those required for antiviral activity.[8]

Resistance Profile

The resistance profile of atazanavir has been characterised in isolates from antiretroviral-naive or -experienced patients participating in clinical studies who failed treatment with an atazanavir-containing regimen,[12,13] in clinical isolates resistant to other PIs,[5,9,10,14,15] and *in vitro* in laboratory strains.[9]

Atazanavir-Resistant Clinical Isolates

- Resistance to atazanavir emerged infrequently in phase II and III clinical trials (see section 3) and was found in about 6% of treated patients and about 20% of all treatment failures from atazanavir-containing regimens.[12]
- The I50L substitution was demonstrated to be the signature mutation for atazanavir resistance and was present in all 19 isolates recovered from patients who experienced virological failure and who were treatment-naive at baseline and received atazanavir as the sole PI (treatment duration 24–81 weeks).[12] Substitutions were also found at A71V, G73S and K45R in 11, 5 and 4 isolates, respectively. Resistance appeared to be specific for atazanavir (median 8.8-fold change in susceptibility; range 3.5–36.6) as the susceptibility to six other PIs remained unchanged or slightly increased from baseline.
- The I50L substitution was not present in any of the isolates from eight treatment-experienced (but atazanavir-naive) patients who failed treatment with atazanavir plus saquinavir in study AI424-009.[12] Resistance in these isolates was acquired by the accumulation of several primary and secondary mutations, including I84V, observed in the development of resistance to other PIs.
- Recombinant viruses containing I50L and the I50L/A71V mutations had decreased sensitivity to atazanavir *in vitro* and were significantly growth impaired. There was no evidence of cross-resistance between atazanavir and amprenavir despite the known relationship between I50V substitution and amprenavir resistance.[13]

Clinical Isolates Resistant to Other Protease Inhibitors

- Clinical isolates (n = 58[14] and 63[10]) with various patterns of resistance to other PIs (nelfinavir, saquinavir, indinavir, ritonavir and amprenavir) displayed a distinct pattern of resistance to atazanavir. Sensitivity to atazanavir (a ≤5-fold change in susceptibility) was present in 38 (60%) of the isolates in one report, and 34 (89%) of these were in isolates resistant to only 1–3 of the other PIs[10] even in the presence of key signature substitutions associated with development of resistance to other PIs (10, 71, 82, 84 and 90 residues).

• There was a loss of sensitivity to atazanavir when isolates had very high resistance levels for >3 PIs and a significant number of mutations.[10,14] While atazanavir, saquinavir and amprenavir provided similar coverage (60%) in one report,[10] there was a general lack of cross-resistance between atazanavir, saquinavir, ritonavir, nelfinavir and amprenavir. Of the four isolates resistant to atazanavir (and resistant to any 1–3 other PIs), three showed some (6-fold) cross-resistance to ritonavir, indinavir and nelfinavir, while a single isolate showed 14-fold cross-resistance to nelfinavir only.[10]

• Atazanavir susceptibility changes of ≤6-fold were present in 98% of 134 clinical isolates (from patients previously untreated with atazanavir) resistant to one or two other PIs, compared with 58% resistant to 3–4 PIs.[5] In isolates cross-resistant to all five PIs (nelfinavir, saquinavir, indinavir, ritonavir and amprenavir) atazanavir resistance increased 9-fold or higher.

• No single amino acid substitution was predictive of reduced susceptibility to atazanavir in 198 clinical isolates from atazanavir-naive, but PI-experienced, patients.[15] A >4-fold increase in the EC_{50} for atazanavir was noted in 25 of 28 (89%) isolates which had at least five of seven substitutions correlated with decreased susceptibility to atazanavir. With other PIs (saquinavir, ritonavir, indinavir, nelfinavir and amprenavir) only two mutations produced loss of sensitivity in some cases, while in contrast the majority (79%) of isolates with <5 substitutions remained sensitive (≤4-fold increase in EC_{50} threshold) to atazanavir.

• A larger analysis of 943 clinical isolates from atazanavir-naive, but PI-experienced, patients confirmed a distinct resistance profile for atazanavir with loss of sensitivity associated with the presence of 5 of 14 key amino acid substitutions.[16] Again, there was a clear trend towards loss of susceptibility as isolates displayed increasing levels of cross-resistance to multiple PIs. Atazanavir sensitivity (defined as ≤3-fold increase in EC_{50} relative to the reference strain) was retained in 86% of the 214 isolates resistant to 1–2 of the other PIs and by 25% of the 195 isolates resistant to 3–4 PIs. Of the 176 atazanavir-resistant isolates (from the panel of isolates resistant to 1–4 PIs) 23% had a >10-fold increase in EC_{50} compared with 24%, 46%, 39%, 57%, 60% and 42% in similar analyses of isolates resistant to amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir, respectively.

Effects on Lipids

In clinical trials in antiretroviral-naive and -experienced patients, atazanavir had no effect on total cholesterol (TC), fasting low density lipoprotein-cholesterol (LDL-C) and fasting triglyceride (TG) levels compared with other PIs which caused prompt, substantial and sustained increases in these lipid levels (see section 3 for clinical trial design).[4,17-20]

Antiretroviral-Naive Patients

• In a dose-ranging study (AI424-007), 48 weeks' treatment with nelfinavir 750mg three times daily caused significantly greater increases from baseline in mean lipid levels than atazanavir 400mg once daily (TC, 27.8% vs 6.8%; fasting LDL-C, 31.1% vs −7.1%; fasting TG, 42.2% vs 1.5%; all $p < 0.001$).[4] All patients received didanosine and stavudine in addition to their randomised treatment. After 48 weeks, 18% of the patients receiving nelfinavir met the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for commencing lipid-lowering therapy compared with 6% of the patients receiving atazanavir.[21]

• In study AI424-008, after 48 weeks, patients receiving nelfinavir 1250mg twice daily had significantly greater increases from baseline in mean lipid levels compared with atazanavir 400mg once daily recipients (TC, 25% vs 5%; fasting LDL-C, 23% v 5%; fasting TG, 50% vs 7%; all $p < 0.05$).[21] All

patients received stavudine and lamivudine in addition to their randomised treatment. Cumulative data from studies AI424-008 and -044 showed minimal change in lipid levels for atazanavir recipients after 108 weeks (mean percentage change data not reported).[19]

- In another study (AI424-034), patients receiving atazanavir 400mg once daily showed a significantly improved lipid profile compared to patients receiving efavirenz 600mg once daily.[17] All patients also received zidovudine and lamivudine. After 48 weeks' treatment, patients receiving atazanavir had significantly reduced elevations in TC (2% vs 21%), fasting LDL-C (1% vs 18%) and fasting TG (−9% vs 23%) compared to patients receiving efavirenz ($p < 0.0001$ in each case). Patients receiving efavirenz also showed a slight increase in high-density lipoprotein-cholesterol (HDL-C) compared to those receiving atazanavir (24% vs 13%).

Antiretroviral-Experienced Patients

- After 48 weeks in study AI424-009, mean changes from baseline in TC, fasting LDL-C and fasting TG were 1%, −0.6% and −4.8%, respectively, in patients receiving atazanavir 400mg and saquinavir 1200mg, both once daily, compared with 10.7%, 23.2% and 93% in patients being treated with ritonavir 400mg and saquinavir 400mg, both twice daily (both treatment groups also receiving zidovudine and lamivudine).[18] The differences were significant for fasting LDL-C and TG ($p < 0.05$ and $p < 0.001$, respectively) in favour of the atazanavir and saquinavir combination. Mean increases from baseline for HDL-C were similar at 11.8% and 10.6% for atazanavir/saquinavir and ritonavir/saquinavir, respectively.[22]
- Patients in study AI424-044 (extension of AI424-008) who switched to atazanavir from nelfinavir (and continued with stavudine and lamivudine) had significant ($p < 0.0001$) mean percentage reductions from baseline in lipid levels, toward pre-antiretroviral treatment levels, by 12 weeks and these levels were maintained at 24 weeks (TC −16%; fasting LDL-C −20%; and fasting TG −25% vs baseline).[19] Mean HDL-C increased by 5% for the switched patients (significant at week 12, $p < 0.05$, but not at week 24). The percentage of patients who switched to atazanavir who had 'undesirable' lipid parameters after 12 weeks for TC and LDL-C (≥240 and ≥130 mg/dL, respectively, as defined by NCEP ATP III) decreased to levels similar to those in patients who had only received atazanavir-based therapy (from 32% to 10% and from 55% to 22% for TC and LDL-C, respectively).[23]
- Interim results from two studies, AI424-043 and -045 showed that atazanavir-containing regimens were associated with a decrease from baseline in fasting LDL-C (a co-primary efficacy objective in AI424-043).[20] After 24 weeks, mean fasting LDL-C decreased by 6% in patients receiving atazanavir 400mg once daily (plus 2 NRTIs) compared with an increase of 8% in those receiving lopinavir 400mg/ritonavir 100mg ($p < 0.0001$). After 16 weeks, mean fasting LDL-C decreased by 8% and 10% in patients in the second trial who received regimens containing atazanavir 300mg/ritonavir 100mg daily or atazanavir 400mg/saquinavir 1200mg daily, respectively, compared with a small increase of 1% in patients receiving a regimen containing lopinavir 400mg/ritonavir 100mg twice daily. In both trials the effect on TC and TG was superior for the atazanavir-containing regimens compared with the comparator regimens although this difference was not significant at 16 weeks in AI424-045.

Effects on Glucose and Insulin

- In antiretroviral-naive patients receiving atazanavir 400mg ($n = 404$) or efavirenz 600mg ($n = 405$) once daily, in combination with zidovudine and lamivudine, mean fasting glucose and insulin levels were similar to baseline levels after 48 weeks for both atazanavir and efavirenz treatment groups.[17] Mean fasting glucose increased from 90

to 93 mg/mL for atazanavir and 90 to 94 mg/mL for efavirenz. Mean fasting insulin increased from 11.3 to 12.3 μU/mL for atazanavir and 9.9 to 11.5 μU/mL for efavirenz.

- In antiretroviral-experienced patients fasting insulin and glucose levels were similar after 24 weeks to baseline in patients receiving regimens containing atazanavir 400mg once daily or lopinavir 400mg/ritonavir 100mg twice daily.[20]
- *In vitro* studies showed atazanavir did not inhibit glucose transport (associated with the development of insulin resistance) through insulin-mediated GLUT-4.[17]

2. Pharmacokinetic Profile

The pharmacokinetic profile of oral atazanavir has been assessed in a series of single-, multiple-, and ascending-dose studies in healthy volunteers and HIV-infected patients. There does not appear to be a clinically significant effect of age or sex on single-dose pharmacokinetic parameters.[24] Published data on the distribution and metabolism of atazanavir are limited at present.

Absorption and Distribution

- In several studies of healthy volunteers (n = 10–30) receiving multiple doses of atazanavir 400mg once daily, taken with a light meal for 6–14 days, values for C_{min} ranged from 149 to 219 ng/mL; peak plasma concentration (C_{max}), 2918–5867 ng/mL; time to C_{max} (t_{max}), 2–4 hours; and area under the plasma concentration-time curve during a dosage interval at steady state (AUC_τ), 18 590–33 500 ng • h/mL.[6,25-31]
- Following administration of single doses of atazanavir to healthy volunteers, C_{max} and AUC_τ values increased in a dose-proportional manner. However, in 31 treatment-naive patients receiving multiple doses of atazanavir 200, 400 or 500mg once daily (ratio of 1 : 2 : 2.5), increases in AUC_τ after 29 days were in the ratio 1 : 1.8 : 2.1 and increases in C_{max} were in the ratio of 1 : 1.7 : 2.2.[32]
- In healthy volunteers, the bioavailability of a capsule formulation relative to that of an oral solution was about 60% in a single-dose study (100, 300, 600, 900 and 1200mg, n = 40)[33] and about 68% in a multiple-dose study (200, 400, 500 or 600mg once daily for 14 days, n = 24).[7]
- There is a clinically relevant increase in the absorption of atazanavir when the drug is administered with food. In 32 healthy volunteers who received a single 400mg dose of atazanavir, AUC was increased from fasting levels by 70% and 35% in patients who had also received a light- or high-fat meal and interpatient variability in drug levels decreased from 69% (fasting) to 37% and 43%, respectively.[7,34]
- Protein binding of atazanavir to albumin and α_1-acid glycoprotein is about 86%.[32] Hollow-fibre unit experiments showed that for atazanavir, like other PIs, the concentration of nonprotein-bound (free) drug must exceed a threshold of 4 × EC_{50} (≈ EC_{95}) for the majority of the dosage interval, for maximal suppression of viral replication to occur.[5,11] In healthy volunteers, after administration of single doses >300mg or dosages of ≥400mg taken once daily (with a light snack or meal), plasma atazanavir concentrations remained above the EC_{50} values (data not reported) for >24 and 36 hours (at steady state), respectively.[4,33] At steady state, following administration of 400mg to healthy volunteers, atazanavir C_{min} was generally greater than the target 90% protein-binding adjusted inhibitory concentration (IC_{90}) value for >24 hours.[6,32,34]
- Atazanavir showed good penetration into semen with median concentrations ranging from 132.3 to 382.7 ng/mL for patients who received an atazanavir dose of 400 (n = 5) or 600mg (n = 12) once daily for 12 weeks, respectively.[35] The semen : plasma ratios ranged from 0.11 to 4.4 (median, 0.13) for the 400mg dosage and 0.09 to 1.5 (median, 0.14) for the

600mg dosage. In addition, cerebrospinal fluid (CSF) concentrations in a separate substudy (n = 7) with the same atazanavir dosages were all ≥2.5 ng/mL and several-fold above the mean EC_{50} (1 ng/mL) for wild-type virus isolated in treatment-naive patients.[35]

- Apparent volume of the central compartment (V_c) was 187 and 109L, and first-order absorption rate constant (k_a) was 1.45 and 6.48/h for two groups of patients (slow and rapid absorbers, respectively) receiving atazanavir 400 or 600mg once daily (all values estimated from a model developed using data from fasted healthy volunteers in a dose-escalation study).[36]

Metabolism and Elimination

- Atazanavir is metabolised predominately by hepatic cytochrome P450 (CYP)3A isoenzymes[32] and undergoes biliary elimination.[20] Three minor metabolites are formed which have no anti-HIV activity. Minimal renal elimination occurs for atazanavir or its metabolites. Mean half-life ($t_{1/2}$) values were 2.81, 2.82, and 6.14 hours in healthy volunteers (n = 24) who received single oral atazanavir doses of 100, 300 or 600mg, respectively. [7,33]
- After multiple doses of 200, 400, 500 or 600mg once daily, mean $t_{1/2}$ values were 4.9, 5.4, 5.7 and 9.8 hours, respectively, in 24 healthy volunteers in a randomised, double-blind, placebo-controlled trial.[7] Similarly, in a study in which 32 healthy volunteers who received atazanavir 200 or 400mg once daily with a light meal, the mean $t_{1/2}$ was 4.53 and 5.28 hours.[25]
- In other studies of healthy volunteers (n = 10–30) receiving atazanavir 400mg once daily, taken with a light meal for 6–14 days, mean $t_{1/2}$ values ranged from 5.53 to 8.85 hours.[6,27,28,30,31]
- Clearance was estimated at 36.7 L/h for the 200mg dose and 25.2 L/h for the 400 or 600mg dosages.[36]

Drug Interactions

Atazanavir is a moderate inhibitor of CYP3A[32] with inhibitory constant (K_i) values ranging from 2.2 to 2.7 nmol/L (similar to amprenavir, indinavir, nelfinavir, ritonavir and saquinavir).[6,8-10,32] Several studies have investigated potential interactions between atazanavir, other antiretroviral drugs and other drugs with an effect on the CYP system.

- Plasma atazanavir exposure was increased several-fold by concomitant ritonavir (a potent CYP3A inhibitor) in a study of healthy volunteers receiving atazanavir 400mg (n = 16) once daily, with a light meal, initially as monotherapy for 6 days, followed by concomitant ritonavir 100 or 200mg once daily for 10 days.[25] For patients receiving concomitant ritonavir 100mg, C_{max} increased from 5367 to 7754 ng/mL, t_{max} was unchanged at 2.25 hours, C_{min} increased from 159 to 1023 ng/mL and AUC_τ increased from 29 357 to 70 345 ng • h/mL.
- Plasma levels of atazanavir and ritonavir, taken as salvage therapy (both once daily with unchanged NRTIs from the previous regimen) for 2 weeks, decreased by about 25% and 10–25%, respectively, 4 weeks after the introduction of tenofovir 300mg once daily in ten HIV-infected males.[37] No mechanism for this interaction was suggested.
- Thirty-one healthy patients receiving atazanavir 400mg once daily had reductions in C_{max} (59%), AUC (74%) and C_{min} (99%), 14 days after the addition of efavirenz (a CYP3A4 inducer) 600mg once daily.[28]
- Atazanavir 600mg coadministered with efavirenz 600mg for 14 days (days 7–20) reduced the geometric mean AUC for atazanavir by 21% in healthy volunteers.[27] However, atazanavir 300mg coadministered with ritonavir 100mg and efavirenz 600mg (all once daily) increased the atazanavir AUC by 39% compared with atazanavir 400mg alone.[27]

• No clinically significant interactions were noted when atazanavir was administered 1 hour after stavudine and didanosine in healthy volunteers. However, simultaneous administration resulted in an 89.3% decrease in mean atazanavir C_{max} and an 87% decrease in atazanavir AUC (perhaps due to the antacid in the buffered formulation of didanosine).[7,34] Atazanavir, lamivudine and zidovudine can be coadministered without dose modification.[38]

• In combination with atazanavir 400mg (and a high-fat meal), the AUC_τ of saquinavir (taken as 800, 1200 or 1600mg once daily as a soft-gel formulation) was increased 5.4- to 7.1-fold in 24 healthy volunteers whereas the pharmacokinetics of atazanavir were not affected by coadministration with saquinavir-soft gel.[34]

• Coadministration of atazanavir with rifabutin[30] or clarithromycin[29] resulted in increases in systemic exposure (AUC) to rifabutin (2-fold) and clarithromycin (1.9-fold). No dose adjustment of a combined oral contraceptive (Ortho-Novum® 7/7/7) was necessary when it was coadministered with atazanavir 400mg once daily.[27] Coadministration of atazanavir with ketoconazole did not have a clinically relevant effect on the pharmacokinetics of atazanavir.[6]

3. Therapeutic Trials

Several multinational, randomised and active-controlled comparative phase II (AI424-007[4], -008/044[19,21,39,40] and -009[18]) and phase III (AI424-034,[17] -043 and -045) studies have evaluated the efficacy of atazanavir-containing regimens in both antiretroviral-naive and -experienced patients with HIV infection. Two of the studies have been published,[4,18] but most have been reported as abstracts only[17,19,21,39,40] while details of studies AI424-043 and -045 have been reported in a briefing paper to the US FDA.[20] The earlier studies were either single (AI424-007, -008 and -009) or double-blind (AI424-034), whereas the trials involving antiretroviral-experienced patients were mostly nonblind (AI424-043, -044 and -045).

Typical inclusion criteria for trials in antiretroviral-naive patients included plasma HIV RNA levels of ≥2000 copies/mL and CD4+ cell counts of ≥100 cells/mm^3 (or ≥75 cells/mm^3 if no prior AIDS-defining diagnosis) at baseline. Mean HIV RNA levels for antiretroviral-naive patients at study entry ranged from 4.6[21] to 4.89 log_{10} copies/mL (≈80 000 copies).[17] Treatment-experienced patients were required to have failed on previous HAART regimens (see below).

The primary endpoint for all studies except AI424-034 was the change from baseline in plasma HIV RNA level (observed cases). Secondary endpoints were the proportion of patients with plasma HIV RNA levels of <400 or <50 copies/mL (intent-to-treat, non-completer = failure analysis) and the change from baseline in CD4+ cell count (observed cases). Study AI424-034 alone was sufficiently powered for the proportion of patients with plasma HIV RNA levels of <400 copies/mL to be the primary endpoint.

Antiretroviral-Naive Patients

• In the dose-ranging study (AI424-007)[4] 420 patients were randomised in a 1 : 1 : 1 : 1 manner to receive atazanavir 200, 400 or 500mg once daily or nelfinavir 750mg three times daily, initially as monotherapy for 2 weeks, and then in combination with stavudine (40mg twice daily) plus didanosine (400mg once daily) for a further 46 weeks. Patients intolerant of stavudine or didanosine were able to substitute zidovudine or lamivudine, respectively. During the initial monotherapy phase a rapid mean reduction in plasma HIV RNA levels from baseline (4.73 log_{10} copies/mL) of about 1.4 log_{10} copies/mL occurred after 2 weeks and was similar across all treatment groups. Atazanavir-based combination therapy also produced a similar response to the nelfinavir-based regimen. A rapid mean decrease

from baseline in viral load of about 2.5 $\log_{10}$ copies/mL occurred by week 16 and was sustained at 48 weeks across all four arms of the study (see figure 1).

- The mean proportion of patients obtaining HIV RNA levels <400 copies/mL and <50 copies/mL after 48 weeks was broadly similar across all combination treatment groups (see figure 2).[4] CD4+ cell count increased continuously in all groups. Mean increases from baseline in CD4+ cell count at 48 weeks were 220, 221 and 208 cells/mm^3 in the patient groups receiving atazanavir 200, 400 and 500mg once daily, respectively, and 185 cells/mm^3 in the nelfinavir group.

- A second study (AI424-008) randomised 467 patients in a 2 : 2 : 1 scheme to receive atazanavir 400 or 600mg once daily or nelfinavir 1250mg twice daily both in combination with stavudine (40mg twice daily) and lamivudine (150mg twice daily).[21,39] Mean reductions from baseline in viral load of 2.51 and 2.58 $\log_{10}$ copies/mL were achieved in patients receiving atazanavir 400 or 600mg, respectively, compared with a 2.31 $\log_{10}$ copies/mL reduction in the nelfinavir group ($p < 0.05$ for atazanavir 600mg vs nelfinavir).[39] Sixty-four percent and 67% of atazanavir 400 and 600mg recipients, respectively had HIV RNA levels of ≤400 copies/mL at 48 weeks, compared with 53% of nelfinavir recipients. Co-infection with hepatitis B or C virus did not significantly affect the level of HIV RNA suppression.[40] After 48 weeks mean CD4+ cell counts increased from baseline by 234, 243 and 211 cells/mm^3 in the atazanavir 400 or 600mg and nelfinavir groups, respectively.[39]

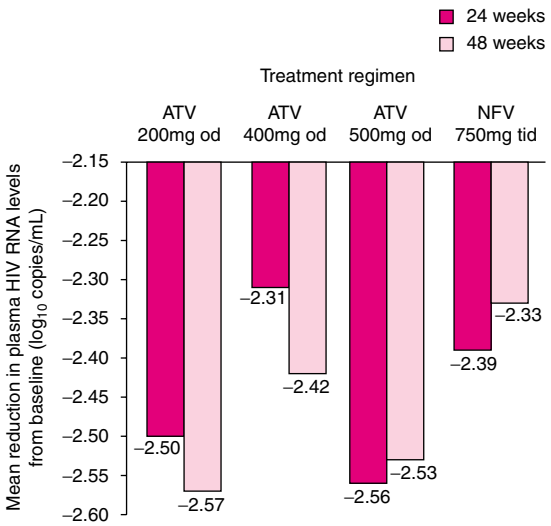


Fig. 1. Mean reduction from baseline in plasma HIV RNA levels (observed cases) with atazanavir (ATV) or nelfinavir (NFV) in combination with stavudine plus didanosine after 24 and 48 weeks in treatment-naive patients with HIV infection. In a multicentre, single-blind dose-ranging phase II trial (AI424-007)[4] patients were randomised to receive once-daily (od) atazanavir 200 (n = 104), 400 (n = 103) or 500mg (n = 110) or nelfinavir 750mg (n = 103) three times daily (tid). All patients received atazanavir or nelfinavir monotherapy for two weeks after which didanosine 400mg once daily plus stavudine 40mg twice daily were added for a further 46 weeks. Bars show the mean reduction in plasma HIV RNA levels after 24 (n = 73, 72, 68 and 74) and 48 (n = 67, 64, 60 and 65) weeks.

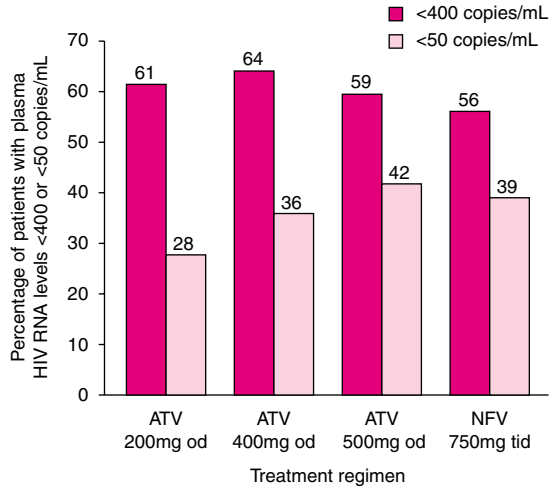


Fig. 2. Percentage of patients with plasma HIV RNA levels <400 or <50 copies/mL is similar with atazanavir (ATV) or nelfinavir (NFV) in combination with stavudine plus didanosine after 48 weeks in treatment-naive patients with HIV infection (intent-to-treat, non-completer = failure analysis). In a multicentre, single-blind dose-ranging phase II trial (AI424-007)[4] patients were randomised to receive once-daily (od) atazanavir 200 (n = 104), 400 (n = 103) or 500mg (n = 110) or nelfinavir 750mg (n = 103) three times daily (tid). All patients received atazanavir or nelfinavir monotherapy for two weeks after which didanosine 400mg once daily plus stavudine 40mg twice daily were added for a further 46 weeks. Bars show the percentage of patients with plasma HIV RNA levels <400 or <50 copies/mL after 48 weeks (n = 83, 78, 79 and 82).

• The virological response described in the above study was maintained in patients who remained on atazanavir for 72 weeks (median) and then became eligible for an extension phase (AI424-044).[19] After a further 24 weeks, 80% and 58% of patients (n = 139) who remained on atazanavir 400mg once daily had HIV RNA levels <400 and <50 copies/mL, respectively. In addition the median CD4+ cell count increased from 472 at study entry to 556 cells/mm^3.

• A recent randomised (in a 1 : 1 manner) trial (AI424-034)[17] with 810 patients compared atazanavir 400mg once daily with efavirenz 600mg once daily, both with a fixed-dose combination of zidovudine and lamivudine. In this study 70% of patients receiving atazanavir had HIV RNA levels of <400 copies/mL at 48 weeks compared with 64% of those receiving efavirenz; HIV RNA levels of <50 copies/mL were achieved in 32% and 37% of patients, respectively. The change in plasma HIV RNA levels from baseline after 48 weeks were not reported. No statistical difference was demonstrated in the virological responses for either treatment, or between responses achieved in patients with higher HIV RNA levels (>100 000 copies/mL) or less advanced disease at baseline. Mean CD4+ cell count increased by 176 cells/mm^3 from a baseline of 314 cells/mm^3 in patients receiving atazanavir compared with an increase of 160 cells/mm^3 from a baseline of 330 cells/mm^3 in those receiving efavirenz.

Antiretroviral-Experienced Patients

• An early phase II trial (AI424-009) randomised 85 patients with previous virological failure to receive either atazanavir (400 or 600mg once daily) plus saquinavir (400mg twice daily), or ritonavir (400mg twice daily) plus saquinavir (400mg twice daily).[18] All patients also received zidovudine and lamivudine. After 48 weeks, the mean reduction in viral load in all three arms was similar (1.19–1.66 $\log_{10}$ copies/mL) with similar proportions of patients in each group (29%–41%) achieving HIV RNA levels of <400 copies/mL or a >1.0 $\log_{10}$ copies/mL decrease in HIV RNA levels. Mean increase from baseline in CD4+ cell counts ranged from 55 to 149 cells/mm^3 in the three treatment groups.

• Patients completing study AI424-008[21,39,40] comparing atazanavir with nelfinavir (each with stavudine plus lamivudine) were eligible for inclusion in a switch trial after 72 weeks (AI424-044).[19] Sixty-three patients switched from nelfinavir to atazanavir 400mg once daily and after 24 weeks, 86% of these patients had HIV RNA levels of <400 copies/mL compared with 71% prior to the switch. The proportion of patients with a viral load <50 copies/mL increased from 50% to 59%. The increase in the proportion of patients reaching these endpoints was similar in both the patients who were switched from nelfinavir and in those who had remained on atazanavir 400 or 600mg. By week 24, the median CD4+ cell count had increased from 543 to 584 cells/mm^3 for patients switched to atazanavir from nelfinavir.

• In study AI424-043 300 patients who had failed on previous antiretroviral treatments, including one PI-containing regimen, were randomised to receive atazanavir 400mg once daily or twice-daily lopinavir 400mg plus ritonavir 100mg (data available from the first 229 patients).[20] All patients also received two NRTIs (based on physician choice and phenotypic susceptibility data from the patient's viral isolate). A prompt decline in mean HIV RNA level of about 1.62 $\log_{10}$ copies/mL from a baseline of 4.15 $\log_{10}$ copies/mL occurred after 4 weeks in patients receiving the atazanavir-based regimen (n = 114) and was sustained at −1.73 $\log_{10}$ copies/mL after 24 weeks. In contrast, patients receiving lopinavir/ritonavir (n = 115), after 24 weeks had a mean reduction in viral load of 2.16 $\log_{10}$ copies/mL from a baseline of 4.19 $\log_{10}$ copies/mL. The time-averaged difference between the regimens was

0.31 log_{10} copies/mL (97.5% confidence interval: 0.06, 0.55) in favour of lopinavir/ritonavir. After 24 weeks, 61% of patients receiving atazanavir had HIV RNA levels of <400 copies/mL compared with 81% of those receiving lopinavir/ritonavir. Mean CD4+ cell count increased by 101 and 121 cells/mm^3 after 24 weeks from median baseline levels of 279 and 249 cells/mm^3 in patients receiving the atazanavir- and lopinavir-based regimens, respectively.

• In an ongoing, randomised and multinational study (AI424-045)[20] antiretroviral-experienced patients were randomised to receive atazanavir 300mg/ritonavir 100mg daily (n = 120), atazanavir 400mg/saquinavir 1200mg daily (n = 115) or lopinavir 400mg/ritonavir 100mg twice daily (n = 123). All patients in this study were required to have failed at least two prior treatment regimens that in total included at least one member of each class of HIV drugs (NNRTIs, NRTIs and PIs). Patients in each treatment arm also received another PI, tenofovir 300mg daily and an NRTI. Mean reductions in HIV RNA levels from baseline after 24 weeks were 1.86, 1.52 and 1.89 log_{10} copies/mL, respectively. The time-averaged difference between the atazanavir/ritonavir and lopinavir/ritonavir regimens was 0.14 (97.5% confidence interval: −0.09, 0.37) in favour of lopinavir with ritonavir. The proportions of patients with a viral load of <400 copies/mL after 24 weeks were 64%, 44% and 62% in patients receiving atazanavir/ritonavir, atazanavir/saquinavir and lopinavir/ritonavir, respectively. Mean increases in CD4+ cell counts after 16 weeks were 84, 55 and 110 cells/mm^3 from median baseline levels of 317, 286 and 282 cells/mm^3, respectively.

4. Tolerability

• Atazanavir was generally well tolerated in all clinical trials, with the type and frequency of adverse events by 24 (AI424-043, -045),[20] 48 (AI424-007, -008, -009 and -034)[4,17,18,39] and 108 (AI424-044) weeks[19] similar to those reported for recipients of all comparator regimens.

• In the dose-ranging trial, 7% of the 410 treated patients discontinued treatment because of adverse events during 48 weeks' treatment (5%, 6%, 10% and 7% in atazanavir 200, 400, 500mg once daily and nelfinavir 750mg three times daily, respectively).[4] In the continuation study, 3% of the nelfinavir patients who switched (after a median of 72 weeks) to atazanavir 400mg once daily (for a median further 36 weeks) discontinued treatment because of an adverse event.[19]

• The most common (≥20%) clinical adverse events in the dose-ranging trial with antiretroviral-naive patients are shown in figure 3.[4] In this trial nausea (25–35%) and infection (46–60%) were the most common adverse events reported by patients receiving atazanavir. Diarrhoea occurred less frequently with atazanavir (23–30%) than with nelfinavir (61%) [$p < 0.001$]. Diarrhoea occurred less frequently in treatment-experienced patients receiving atazanavir 400mg once daily than in those receiving ritonavir 400mg twice daily (31% vs 48%, no p value reported; all patients were also receiving saquinavir).[18] Similarly diarrhoea was reported less frequently, after 16 weeks, in treatment-experienced, atazanavir/ritonavir recipients than in lopinavir/ritonavir recipients (3% vs 10%; no p value reported).[20] In the second phase II study (AI424-008), the incidence of diarrhoea was significantly lower in treatment-naive patients receiving atazanavir 400mg or 600mg than in those receiving nelfinavir (20% vs 15% vs 56%, $p < 0.0001$ for both atazanavir doses versus nelfinavir).[39] Switching from nelfinavir after 72 weeks was associated with a low incidence of diarrhoea (2%), whereas 52% of these patients had experienced diarrhoea prior to the switch.[19]

• Nausea occurred more frequently in patients receiving atazanavir 400mg once daily than in those receiving nelfinavir (35% and 18%, respectively, p

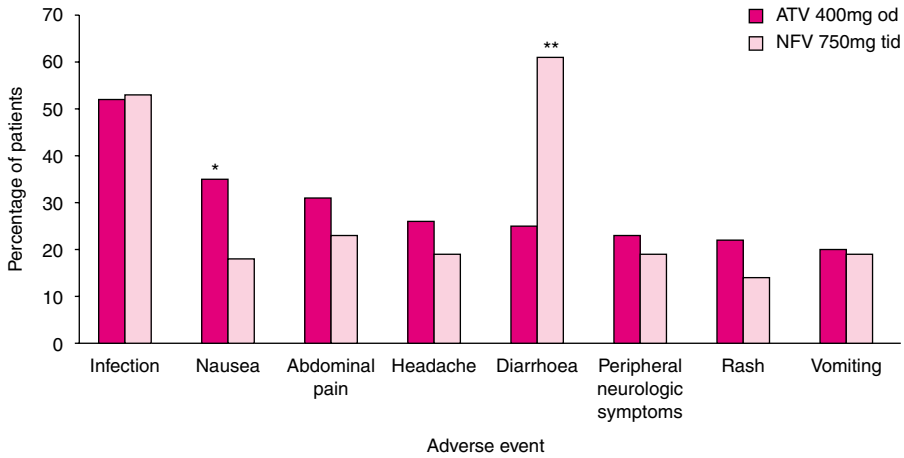


Fig. 3. Tolerability profiles of atazanavir (ATV) and nelfinavir (NFV) in combination with stavudine plus didanosine after 48 weeks in treatment-naive patients with HIV infection. In a multicentre, single-blind dose-ranging phase II trial (AI424-007)[4] patients were randomised to receive once-daily (od) atazanavir 200 (n = 104), 400 (n = 103) or 500mg (n = 110) or nelfinavir 750mg (n = 103) three times daily (tid). All patients received atazanavir or nelfinavir monotherapy for two weeks after which didanosine 400mg once daily plus stavudine 40mg twice daily were added for a further 46 weeks. Bars show the percentage of patients with the most common (≥20%) adverse events after 48 weeks in regimes containing atazanavir 400mg daily or nelfinavir 750mg three times daily. Data for atazanavir 200 and 500mg is not shown. * $p < 0.01$ and ** $p < 0.0001$ atazanavir vs nelfinavir.

< 0.01)[4] although this was not confirmed in a subsequent trial (21% and 18% for atazanavir 400mg once daily and nelfinavir 1250mg twice daily, respectively).[39] Rash (6%) and dizziness (2%) occurred less frequently in atazanavir 400mg once daily recipients than with efavirenz 600mg once daily recipients (10% and 6%, respectively, $p < 0.05$).[17]

- Lactic acidosis occurred in similar numbers of patients in all treatment groups of the dose-ranging trial (ten patients with atazanavir and two with nelfinavir) causing three deaths in atazanavir-treated patients and one in a nelfinavir recipient.[4] Lipodystrophy, grades 1 or 2 in the majority of cases, was infrequent (4%, 9%, 2% and 3% in the atazanavir 200-, 400-, and 500mg groups and the nelfinavir group, respectively).[4]

- Jaundice (6–12%, $p < 0.03$ for all atazanavir doses compared with nelfinavir) and scleral icterus (2–6%) occurred only in atazanavir-treated patients in the dose-ranging trial and was dose-related.[4] Jaundice occurred more frequently in patients who received atazanavir 600mg once daily (22%) compared with those who received atazanavir 400mg (13%) after 108 weeks (median) in cumulative results from the atazanavir/nelfinavir switch study.[19] Across all trials the incidence of grade 2–4 jaundice occurring up to 30 days after the last dose of atazanavir was 5%.[41]

- Unconjugated reversible hyperbilirubinaemia was the most common grade 3–4 laboratory abnormality in all trials, appearing within several days to 1 week, but was not clinically significant and rarely led to discontinuations. In the dose-ranging trial, grade 3–4 elevations in total bilirubin occurred in 20%, 41% and 49% of patients receiving atazanavir 200, 400 or 500mg, respectively, compared with 1% for patients receiving nelfinavir ($p < 0.0001$ for all atazanavir doses compared with nelfinavir).[4] Grade 3–4 hyperbilirubinaemia occurred less frequently in patients switched from nelfinavir (13%) than in those remaining on atazanavir 400mg (26%) or 500mg (44%).[19]

• Grade 3–4 elevations of aspartate transaminase (AST) and alanine transaminase (ALT) occurred in patients receiving atazanavir (4–14%) and in those receiving nelfinavir (4–6%) but these were not correlated with elevations in bilirubin levels (p value not reported).[4] Grade 3–4 transaminitis occurred more frequently in patients who were positive for hepatitis B and/or hepatitis C.[4] AST and ALT elevations of any grade were observed in patients receiving ritonavir/saquinavir combination (68%) and in those receiving atazanavir/saquinavir (56%).[22]

5. Dosage and Administration

• Atazanavir is formulated as a bisulfate salt (100, 150 and 200mg capsules) which is very-to-freely soluble in organic reagents and slightly soluble in water.[6] The pharmacokinetic profile of the drug allows for once-daily oral administration (see section 2). Atazanavir should be administered with food.

• The recommended dosage of atazanavir is 400mg once daily.[42] Dosages of 100 to 1200mg once daily have been used clinically, with 400mg once daily being chosen as the non-boosted dosage for phase III trials, based on efficacy and tolerability data in earlier trials.[36]

• Drug interactions exist between atazanavir and other antiretrovirals (efavirenz, ritonavir, stavudine, didanosine, tenofovir and saquinavir), and with other drugs that effect the hepatic CYP system (see section 2). When coadministered with efavirenz, it is recommended that atazanavir 300mg and ritonavir 100mg be given with efavirenz 600mg (all as a single daily dose with food).[42] When coadministered with didanosine buffered formulations, atazanavir should be given 2 hours before or 1 hour after didanosine.

6. Atazanavir: Current Status

Atazanavir is indicated for the treatment of patients with HIV infection in combination with other anti-HIV therapies. It has a distinct resistance pattern and has shown efficacy when used as the sole PI in treatment-naive patients or in combination with ritonavir or saquinavir in treatment-experienced patients. It was generally well tolerated and did not appreciably increase serum lipid levels after 108 weeks.

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