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Atazanavir/ritonavir-based combination antiretroviral therapy for treatment of HIV-1 infection in adults

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Abstract

In the past 15 years, improvements in the management of HIV infection have dramatically reduced morbidity and mortality. Similarly, rapid advances in antiretroviral medications have resulted in the possibility of life-long therapy with simple and tolerable regimens. Protease inhibitors have been important medications in regimens of combination antiretroviral therapy for the treatment of HIV. One of the recommended and commonly used therapies in this class is once-daily-administered atazanavir, pharmacologically boosted with ritonavir (atazanavir/r). Clinical studies and practice have shown these drugs, in combination with other antiretroviral agents, to be potent, safe and easy to use in a variety of settings. Atazanavir/r has minimal short-term toxicity, including benign bilirubin elevation, and has less potential for long-term complications of hyperlipidemia and insulin resistance compared with other protease inhibitors. A high genetic barrier to resistance and a favorable resistance profile make it an excellent option for initial HIV treatment or as the first drug utilized in the protease inhibitors class. Atazanavir/r is also currently being studied in novel treatment strategies, including combinations with new classes of antiretrovirals to assess nucleoside reverse transcriptase inhibitor-sparing regimens. In this article we review atazanavir/r as a treatment for HIV infection and discuss the latest information on its pharmacology, efficacy and toxicity.

Keywords

antiretroviral therapy; atazanavir; HIV; protease inhibitor; ritonavir

Nearly 30 years since the start of the epidemic, HIV infection remains a major public health problem. Recent surveillance reports estimate that worldwide, 33 million adults are infected with HIV. Annually, there are an estimated 2.7 million new HIV infections occurring and 2 million deaths from HIV disease [201]. Despite these dismal statistics, treatment of HIV infection has improved dramatically due to the development of simple and effective

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combination antiretroviral therapy (cART). Incidence rates of AIDS-defining conditions and HIV-related mortality have decreased considerably with advances in cART [1,2]. Over time, medications for the treatment of HIV have become simpler, less toxic and more potent. There are now several effective cART regimens that carry a burden of only one to three pills dosed once daily and require minimal clinical monitoring. Such advances have allowed for extensive scale-up of cART to primary care clinics in both resource-rich and -poor settings throughout the world.

In the 2010 update on treatment of HIV infection in adults, the International AIDS Society recommended the use of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either the non-nucleoside reverse transcriptase inhibitor efavirenz, a ritonavir-boosted protease inhibitor (PI), or the integrase inhibitor raltegravir for initial cART [3]. For the PI component, they recommend atazanavir or darunavir and alternatively lopinavir or fosamprenavir.

Atazanavir, which is typically administered with low-dose ritonavir (atazanavir/r), has been an important innovation in the treatment of adult HIV infection owing to its ease of dosing, virologic potency, minimal toxicity, high genetic barrier to resistance, favorable resistance profile and lower effect on lipid and glucose metabolism. Important potential limitations to treatment with atazanavir/r are interactions with acid-reducing agents and those mediated by low-dose ritonavir, benign hyperbilirubinemia with jaundice and a rare risk of nephrolithiasis. Atazanavir received US FDA approval for the treatment of adults with HIV-1 infection in 2003 and, since then, it has been widely prescribed throughout the USA and Europe. Additionally, atazanavir/r-based cART has become increasingly available in resource-limited settings. Atazanavir/r is currently being studied in novel HIV treatment strategies, including combinations with a CCR5 inhibitor or an integrase inhibitor, to provide NRTI-sparing treatment options. This article examines the latest reports on the treatment of adults with HIV using atazanavir/r-based cART.

Basic pharmacology & pharmacokinetics

Mechanism of action

Atazanavir is an azapeptide HIV-1 PI that prevents the formation of mature virions through the potent and selective inhibition of viral Gag and Gag–Pol polyprotein processing in HIV-1-infected cells [4].

Pharmacology

Although atazanavir can be administered alone to treatment-naive patients who cannot tolerate ritonavir, it is preferably co-administered with low-dose ritonavir to optimize its pharmacokinetic parameters and efficacy (Table 1) [5]. Therefore, this section will focus on the pharmacology of atazanavir/r, unless otherwise noted.

Absorption—Following oral administration with low-dose ritonavir, atazanavir is rapidly absorbed into the systemic circulation, reaching its peak concentration (C_{max}) in approximately 3 h (T_{max}) and steady-state concentration between days 4 and 8, with approximately 2.3-fold accumulation [6,202]. Atazanavir dissolution and absorption are highly dependent on gastric pH, which has been confirmed through drug-interaction studies with acid-suppressing agents and may explain some of the observed decrease in atazanavir exposure noted in HIV-infected patients compared with healthy volunteers [7].

Food effect—Atazanavir absorption is further optimized when taken with food. After a single 400-mg dose was given to healthy volunteers with a high-fat meal, atazanavir

exposure increased by 35% compared with when taken in the fasting state. Additionally, the presence of food reduced interpatient variability in area under the plasma concentration–time curve (AUC) from 69% in the fasted state to 43 and 37% with a high-fat and light meal, respectively [8,9]. The pharmacokinetic benefit of food was further demonstrated when atazanavir was boosted with ritonavir. Compared with the fasting state, a light meal (336 kcal, 5.1 g fat and 9.3 g protein) increased the atazanavir AUC by 33% and the C_{max} by 40%. Although administration with a high-fat meal (951 kcal, 54.7 g fat and 35.9 g protein) increased the C_{max} by less than 11% and did not significantly impact the AUC, the minimum plasma concentration (C_{min}) and T_{max} increased due to delayed absorption, and the interpatient variability was reduced by approximately 25% [202]. The effect of food on atazanavir/r exposure was confirmed in an HIV-infected population, in whom the atazanavir AUC, C_{max}, and C_{min} decreased by 41, 32 and 53%, respectively, when taken in the fasted state [10]. Therefore, atazanavir should always be administered with food to improve absorption and reduce variability.

Distribution—Atazanavir is highly protein-bound in serum to α-1-acid glycoprotein (AAG) and albumin, 89% and 86%, respectively, and *in vitro* data indicate a higher binding affinity to AAG than albumin [11]. Atazanavir distribution into the tissues is generally low and highly variable. Penetration into seminal fluid was confirmed in 15 HIV-infected men (13 receiving atazanavir/r), with atazanavir seminal fluid concentrations ranging from 0.02 to 0.99 mg/l and a median seminal/blood plasma ratio of 0.1 (interquartile range: 0.08–0.17) [12]. Cerebrospinal fluid (CSF) penetration of atazanavir was evaluated in patients taking atazanavir 300 mg/ritonavir 100 mg once daily and the median atazanavir concentration in CSF:plasma ratio was 0.009 (range: 0.002–000.034) [13]. Population modeling from these data confirmed high inter-patient variability and estimated atazanavir CSF penetration to be 0.74% of the plasma concentration, which may not consistently provide effective antiviral activity in the CSF. The CNS penetration-effectiveness score, proposed by the CHARTER Study Group in 2010 and based on CSF penetration, is 2 (range: 1–4) for atazanavir/r [14]. The sum of the individual CNS penetration-effectiveness scores for each component of a regimen has been correlated to CSF viral load as well as improvements in neuropsychological battery tests among patients with neuropsychiatric impairment at baseline; however, there has been no strong consensus on the accuracy of this score [14–16].

Metabolism & elimination—Similar to other PIs, atazanavir is extensively metabolized in the liver, primarily by cytochrome (CYP450)3A isoenzymes – 3A4 and 3A5 [202]. Atazanavir pharmacokinetics are unfavorably affected by CYP3A5 genetic polymorphisms, although minimally in the presence of ritonavir boosting [17]. Other minor pathways described with atazanavir biotransformation include those of glucuronidation, *N*-dealkylation, carbamate hydrolysis, hydroxylation and dehydrogenation, and at least five inactive atazanavir metabolites have been characterized to date [202,18]. Atazanavir and its metabolites are largely eliminated through biliary excretion with minimal renal involvement. Following a single atazanavir 400-mg dose, 79% was recovered in the feces (20% unchanged) and 13% was recovered in urine (7% unchanged) [202]. Population pharmacokinetic modeling in HIV-infected patients receiving atazanavir/r estimates that atazanavir oral clearance is 7.7 l/h (interindividual variability = 29%) and the median elimination half-life is 8.9 h (range: 4.4–24.9) [19]. Similar results have been reported with other models [20,21]. Among the covariates evaluated in these analyses, ritonavir is uniformly identified to significantly impact atazanavir clearance. This effect is a result of potent inhibition of CYP3A4-mediated hepatic metabolism of atazanavir by ritonavir, as well as its inhibition of the drug efflux transporter, P-glycoprotein (P-gp).

In addition to being a substrate for CYP3A4/5-mediated metabolism, atazanavir is also a substrate for several drug efflux transporters, such as P-gp, multidrug resistance-associated

proteins and breast cancer-resistance protein, as well as human organic cation transporters [22,23]. In addition, atazanavir inhibits CYP3A4, CYP2C8 (weak), P-gp, multidrug resistance-associated proteins, organic anion transporting poly-peptides and uridine-glucuronosyl transferase (UGT)1A1, as well as induces P-gp function and P-gp and MRP1 expression [17,22–24]. Clinically, the relationship between these transporters and atazanavir plays an important role in drug efficacy and toxicity, as they are determinants of the penetration of atazanavir into various tissues in which they are expressed, such as the liver, kidneys and brain [23], as well as of potential drug–drug interactions.

Pharmacology considerations in special populations

Gender-related pharmacokinetic differences have been reported for some PIs such as indinavir, saquinavir, lopinavir and ritonavir [25,26]. Although a 2.4-fold-higher atazanavir AUC was described in women versus men receiving atazanavir along with ritonavir-boosted saquinavir [27], when ritonavir-boosted or unboosted atazanavir is the only PI, no significant gender-related differences in atazanavir pharmacokinetic parameters have been identified [19–21,28].

Placental transfer & pregnancy—Human placental transfer of atazanavir was first described in an HIV-infected Caucasian woman receiving ritonavir-boosted atazanavir during pregnancy [29]. The atazanavir concentration in the maternal plasma just prior to delivery and in the cord blood at delivery was 1515 and 362 ng/ml, respectively. Transplacental passage of atazanavir has since been confirmed in several prospective analyses of HIV-infected pregnant women, in whom the mean ratio of atazanavir concentration in the cord to maternal blood has ranged from 0.14 to 0.2 [30–33]. Given its high protein binding ability and large molecular size, this minimal transfer of atazanavir across the placenta is not surprising. Limited and highly variable passage of atazanavir into breast milk has also been observed in three HIV-infected women [34]. The atazanavir concentration exceeded the wild-type IC_{50} in all breast-milk samples, and the ratios of atazanavir breast milk:plasma concentrations at days 5 and 14 post-partum were 0.07 and 0.09, respectively.

Reduced exposure of some PIs has been reported in the pregnant versus nonpregnant states, sometimes necessitating dose increases during the later stages of pregnancy [35,36]. Inconsistent findings have been reported describing atazanavir exposure during pregnancy. In the first study to evaluate atazanavir pharmaco-kinetics during pregnancy, the mean atazanavir C_{max} was slightly lower in the third trimester compared with post-partum, likely explained by delayed absorption [32]. However, no significant difference between ante- and post-partum AUC or C_{min}, was noted in these 17 HIV-infected pregnant women receiving atazanavir/r 300/100 mg once daily, suggesting no need for dose adjustment during pregnancy. When investigators expanded this study population to include 31 patients, the mean third-trimester and post-partum AUC (29.848 vs 32.389 μg•h/ml) and C_{min} (439 vs 405 ng/ml) parameters remained similar [33]. Based on these findings, Ripamonti and colleagues suggest that dose adjustment of atazanavir during pregnancy is not warranted; however, additional studies suggest caution in this practice, particularly in treatment-experienced patients. In another study of 21 HIV-infected pregnant women receiving atazanavir/r 300/100 mg once daily, third trimester and post-partum pharmacokinetics were compared with nonpregnant, HIV-infected, historical controls [37]. Although the mean atazanavir AUC during the third-trimester was similar to the earlier findings by Ripamonti and colleagues (26.6 vs 29.848 μg•h/ml), this was significantly lower than the mean AUC in historical controls (44.2 μg•h/ml). Furthermore, the mean third-trimester atazanavir AUC fell below the investigators' predefined threshold at the interim analysis, which triggered a protocol-defined dose increase to atazanavir/r 400/100 mg once daily as part of a subsequent

analysis. Although the individual and mean third trimester atazanavir C_{min} values remained above the predefined threshold of 150 ng/ml, they were 21% lower than in the historical controls. The mean AUC and C_{min} levels at approximately 4 weeks post-partum were significantly higher than in the historical controls, suggesting that atazanavir pharmacokinetics had not yet normalized to those obtained in a nonpregnant state. Similar results were described in 37 HIV-infected pregnant women taking atazanavir/r 300/100 mg once daily, 18 of whom were also on tenofovir, which has been shown to decrease atazanavir concentrations by approximately 25% in non-pregnant subjects [31,38]. The median C_{min} was significantly lower during the third trimester than post-partum, though 94.4 and 100% of patients, respectively, achieved C_{min} levels above the therapeutic target (150 ng/ml), regardless of tenofovir co-administration. Of concern though was the median atazanavir AUC, which was also significantly lower during the third trimester compared with post-partum. Notably, only 66.7% of patients in the no tenofovir group and 50% of patients in the tenofovir group achieved the pre-defined AUC target (29.4 μg•h/ml). The investigators intend to further evaluate the impact of pregnancy on atazanavir pharmacokinetics to determine if a dose increase to atazanavir/r 400/100 mg once daily is necessary. Results from these studies evaluating the increased atazanavir dose during pregnancy are pending.

End-stage liver & renal disease—The impact of moderate-to-severe hepatic impairment on atazanavir pharmacokinetics was evaluated in 16 patients with liver disease (14 Child-Pugh B and two Child-Pugh C) following a single atazanavir 400-mg dose [5]. The mean AUC was 42% greater in the patients with hepatic impairment compared with healthy volunteers, and the mean half-life was extended from 6.4 to 12.1 h. In another study of 15 HIV-infected patients with end-stage liver disease (ten Child-Pugh B and five Child-Pugh C) receiving atazanavir 400 mg once daily, median AUC and C_{min} values were similar to those in the historical controls, though notably the interpatient variability in AUC was high and most of the patients were also on concomitant tenofovir and/or acid-suppressing therapy [39]. Furthermore, in 131 patients co-infected with hepatitis C virus (HCV), 73 of whom received ritonavir-boosted atazanavir, the degree of liver fibrosis did not impact atazanavir plasma levels in patients with or without cirrhosis [40]. Although the prescribing information cautions against the use of atazanavir in patients with severe hepatic impairment or the use of ritonavir-boosted atazanavir in patients with any degree of hepatic impairment, its safety and efficacy in this patient population has been suggested in several small studies [39,41,42].

Despite its primarily hepatic route of elimination, atazanavir use should be avoided in treatment-experienced patients with end-stage renal disease requiring hemodialysis. The manufacturer released this warning after performing a pharmacokinetic study with multiple doses of atazanavir 400 mg once daily in 20 HIV-uninfected patients with severe renal impairment, of whom ten required hemodialysis [5,43]. Subjects with renal impairment but not requiring hemodialysis had a 19% increase in mean atazanavir AUC as compared with age-, gender- and weight-matched controls with normal renal function. In those subjects undergoing hemodialysis, although only 2.1% of the administered dose was removed during a 4-hour dialysis session, the mean atazanavir AUC was reduced by 42% on hemodialysis days and 28% on non-hemodialysis days compared with controls. The mechanism of this decrease in atazanavir exposure is unknown, but the investigators postulate reduced gastric acid secretion in hemodialysis patients as one potential cause.

Drug interactions

Owing to the numerous metabolic and transporter pathways in which it is involved, atazanavir/r is implicated in several drug–drug interactions. Only a few select interactions

will be discussed in the context of this article. For a more thorough review of atazanavir drug interactions, consult the atazanavir prescribing information [5], antiretroviral treatment guidelines [3] and/or an up-to-date antiretroviral drug interaction reference, such as the University of Liverpool HIV Drug Interaction website [203].

Tenofovir—The pharmacokinetic interaction between atazanavir and tenofovir was first described in 36 healthy volunteers receiving atazanavir 400 mg once daily [38]. The addition of tenofovir decreased the atazanavir AUC and C_{min} significantly by 25 and 40%, respectively, and thus should not be co-administered with unboosted atazanavir. When boosted with low-dose ritonavir, however, the interaction is largely overcome. Although some studies have documented a sustained decrease in atazanavir AUC by 25% ($p = 0.05$) when given with low-dose ritonavir in the presence of tenofovir [44], **oth**ers have found no significant difference in the atazanavir C_{min} or AUC [45,46]. Therefore, the impact, if any, of tenofovir on ritonavir-boosted atazanavir appears to be of low clinical significance in the absence of other drug interactions, and this combination has demonstrated optimal virologic efficacy in large, prospective, randomized controlled trials [47]. The interaction may be bi-directional, as significant increases in tenofovir C_{min} and AUC in the presence of atazanavir have been reported [48]. These findings have not been consistently reproduced in all pharmaco-kinetic evaluations of tenofovir and atazanavir/r 300/100 mg in HIV-infected subjects [49,50]. The mechanism for this interaction is not fully elucidated, but may occur at the gut level and may be mediated by a drug-transporter pathway.

Acid-suppressing agents—The solubility of atazanavir significantly decreases as intragastric pH increases [5]. Therefore, co-administration of atazanavir with acid-suppressing agents, such as proton pump inhibitors or H_2-receptor antagonists, results in a decrease in atazanavir plasma concentrations. This complex interaction has been evaluated in numerous pharmacokinetic studies and the findings have different implications for treatment-naive versus treatment-experienced patients depending on which class of acid-suppressing agents is used.

When famotidine 40 mg twice daily was given with atazanavir/r 300/100 mg once daily to healthy volunteers, the atazanavir AUC and C_{min} decreased by 18 and 28%, respectively [48]. Although the administration of cola with famotidine did not lessen this interaction, increasing the atazanavir/r dose to 400/100 mg once daily did. When tenofovir was also co-administered with famotidine and atazanavir/r 300/100 mg once daily in healthy subjects, the atazanavir AUC and C_{min} decreased by 21 and 28%, respectively [51]. The interaction was further evaluated in HIV-infected patients receiving atazanavir/r 300/100 mg once daily, famotidine 20 or 40 mg twice daily, with and without tenofovir [52]. When administered with famotidine 20 mg twice daily without tenofovir, the atazanavir C_{min} was unchanged and AUC decreased by 13%. When famotidine 20 mg twice daily was given with tenofovir, or famotidine 40 mg twice daily was given either with or without tenofovir, atazanavir exposure decreased by between 20 and 25%. Simultaneous versus temporal administration did not alter these findings significantly for the higher famotidine dose. Recommendations for the use of atazanavir with H_2-receptor antagonists are summarized in Table 2.

The effect of proton pump inhibitors on atazanavir plasma concentrations is even more pronounced than that of H_2-receptor antagonists. Co-administration of atazanavir/r 300/100 mg once daily and omeprazole 40 mg once daily reduced the atazanavir AUC and C_{min} by 76 and 78%, respectively, in healthy volunteers [53]. Simultaneous administration of cola had no effect, and despite an increase to atazanavir/r 400/100 mg once daily, the AUC and C_{min} were still reduced by 61 and 66%, respectively. In another study, omeprazole 20 mg once daily along with atazanavir/r 300/100 mg was shown to have less of an impact than the

40-mg once-daily dose, but still significantly reduced both the atazanavir AUC and C_{min} by 27–46%, with a temporal separation of 12 h showing a slight benefit [54,55]. Increasing the dose to atazanavir/r 400/100 mg with omeprazole 20 mg once daily, either given 1 or 12 h prior to dosing, still resulted in a reduction of atazanavir AUC and C_{min} by approximately 30% [55]. Recommendations for the use of atazanavir with proton pump inhibitors are summarized in Table 2.

Rationale for ritonavir boosting & clinical efficacy

Several clinical trials and recent reviews have evaluated the efficacy of unboosted atazanavir in ART-naive and experienced patients [56–63]. As current recommendations and routine clinical practice are to use ritonavir-boosted atazanavir in both ART-naive and -experienced patients, we primarily reviewed clinical trial efficacy data of atazanavir/r and comparisons with other ritonavir-boosted PI regimens (Table 3). If a patient has contraindications to ritonavir, then the provider should consider initiating an alternative cART regimen, such as a non-nucleoside reverse transcriptase inhibitor or integrase inhibitor-based therapy.

In addition to providing a pharmacokinetic benefit (as reviewed above and in Table 1), ritonavir boosting of atazanavir improves virologic activity and increases the genetic barrier to resistance. In Bristol-Myers Squibb (BMS) AI424–089, unboosted atazanavir was compared with atazanavir/r in ART-naive patients and a greater proportion of patients receiving atazanavir/r achieved HIV RNA suppression to less than 50 copies/ml by week 48 (75 vs 70%) [64]. Atazanavir/r met the criteria for noninferiority to unboosted atazanavir in virologic response at 48 weeks (lower 95% CI) for the difference in proportions greater than −10%); however, three atazanavir/r-treated patients and ten unboosted atazanavir-treated patients met study criteria for virologic failure. Among these patients, none of those treated with atazanavir/r had major genotypic PI resistance, whereas three of the atazanavir-treated patients had emergence of major PI mutations on therapy. Further evidence of the benefit of ritonavir boosting was provided by two observational studies from clinical cohorts that reported greater virologic and immunologic response to regimens with atazanavir/r compared with unboosted atazanavir [65,66]. Among 443 ART-naive patients at Kaiser Permanente and Group Health Cooperative, treatment with an atazanavir/r-based initial regimen was associated with greater odds of achieving HIV RNA levels of less than 400 copies/ml (odds ratio: 3.24; $p = 0.008$), a greater decrease in HIV RNA (-0.37 $\log_{10}$/ml; $p = 0.03$) and a greater increase in $CD4^+$ T-cell count (+59 cells/μl; $p = 0.01$) compared with unboosted atazanavir [65]. Analysis of 354 patients in the atazanavir ‘Early Access Program’ (BMS AI424–900) observed a higher proportion of patients achieving virologic success (HIV RNA suppression to less than 500 copies/ml) at both week 12 (66 vs 47%) and week 48 (86 vs 64%) for those on atazanavir/r compared with unboosted atazanavir [66]. In adjusted analyses, receiving atazanavir/r was independently associated with an increased probability of achieving virologic success (adjusted hazard ratio: 1.57; 95% CI: 1.19–12.06). As expected, decreased virologic success was associated with clinical AIDS, higher baseline viral load and more PI experience. Despite the strong associations between ritonavir boosting and virologic response, we should interpret findings from these observational studies with caution, as they are subject to selection bias.

Overall, studies have found atazanavir/r-based cART to be highly efficacious with virologic suppression to less than 50 copies/ml achieved in 75–84% of ART-naive patients and 33% of ART-experienced patients [64,67–77]. Immunologic recovery was also excellent with reported increases in $CD4^+$ T-cell count of 171–217 cells/ml from baseline to week 48 in ART-naive patients.

Comparative studies: ART-naive

Two Phase III clinical trials have demonstrated similar efficacy of atazanavir/r to other ritonavir-boosted PIs for initial treatment of ART-naive patients also receiving two NRTIs as part of cART. In the Comparison of Atazanavir/Ritonavir in Naive Subjects in Combination with Tenofovir/Emtricitabine Versus Lopinavir/Ritonavir in Combination with Tenofovir/Emtricitabine to Assess Safety and Efficacy (CASTLE) study (883 patients), ART-naive individuals were randomized to receive either atazanavir/r or lopinavir/ritonavir (lopinavir/r). At 48 weeks, HIV RNA suppression to less than 50 copies/ml was similar between the atazanavir/r and lopinavir/r arms (78 vs 76%; $p > 0.05$); however, at 96 weeks, there was a significant difference in favor of greater virologic suppression among those on atazanavir/r (74 vs 68% $p < 0.05$). At both time points, atazanavir/r met the criterion for noninferiority to the lopinavir/r-based regimen (lower 95% CI for the difference in proportions greater than −10%). Immunologic recovery did not differ between atazanavir/r and lopinavir/r arms with median increases in $CD4^+$ T cells of 268 and 290 cells/ml, respectively, at 96 weeks. In the Atazanavir or Lexiva with Ritonavir and Truvada (ALERT) study (106 patients), participants were randomized to receive either atazanavir/r or fosamprenavir/ritonavir (fosamprenavir/r). After 48 weeks of treatment, there was no significant difference in the proportion of patients with HIV RNA suppression to less than 50 copies/ml (83 vs 75%; $p = 0.34$) between the two arms. $CD4^+$ T-cell count increases were also similar (183 vs 170 cells/ml; $p > 0.05$) for atazanavir/r compared with fosamprenavir/r.

In the large Phase III clinical trial AIDS Clinical Trials Group (ACTG) 5202 (1867 patients), atazanavir/r was compared head-to-head with efavirenz in cART regimens containing two different NRTI combinations: abacavir/lamivudine and tenofovir/emtricitabine [76]. The primary efficacy end point of the trial was time to confirmed virologic failure. Virologic failure was defined as HIV RNA greater than or equal to 1000 copies/ml between 16 and 24 weeks or any HIV RNA level greater than 200 copies/ml after 24 weeks of therapy. By intention to treat analysis, the probability of being free from virologic failure was 83.4% for patients on atazanavir/r compared with 85.3% for patients on efavirenz (difference of 1.9%) in the abacavir/lamivudine arm, and 89 versus 89.8%, respectively, in the tenofovir/emtricitabine arm. Despite a small absolute difference in virologic failure of atazanavir/r compared with efavirenz, it did not meet strict statistical criteria of noninferiority in either NRTI arm (lower 95% CI for the difference in proportions greater than −10%). In addition, the ALTAIR study (322 patients) directly compared atazanavir/r with efavirenz, both given in combination with tenofovir/emtricitabine, and found the two regimens to be noninferior for the primary end point of time-weighted AUC mean change in HIV RNA from baseline to week 48 [78]. Finally, compared with a different non-nucleoside reverse transcriptase inhibitor (nevirapine) in the Atazanavir/Ritonavir on a Background of Tenofovir and Emtricitabine (Truvada) Versus Nevirapine (ARTEN) study (569 patients), atazanavir/r was again non-inferior in terms of virologic efficacy (lower 95% CI for the difference in proportions greater than −12%) [79]. The ARTEN study was an open-label, multicenter international clinical trial that directly compared the efficacy and safety of atazanavir/r with nevirapine combined with tenofovir/emtricitabine.

At the present time, there are two ongoing noninferiority clinical trials comparing initial cART regimens anchored with atazanavir/r and the newest PI, darunavir/ritonavir. Metabolic Evaluation in Treatment-Naives Assessing the Impact of Two Boosted PIs on Lipids and Other Markers (METABOLIK) is a 48-week, Phase IV, multicenter study comparing virologic efficacy, changes in lipids, insulin sensitivity and inflammatory biomarkers among ART-naive patients randomized to atazanavir/r or darunavir/r. ACTG 5257 is a 48-week clinical trial of ART-naive patients randomized to atazanavir/r-, darunavir/r-, or raltegravir-based regimens for initial cART. This study will compare

virologic efficacy between the three regimens and metabolic parameters through the ACTG 5260 substudy.

Comparative studies: ART experienced

In the BMS AI424–045 study, 243 patients with virologic failure to at least two prior cART regimens were randomized to either atazanavir/r or lopinavir/r with tenofovir and one other NRTI [69]. By intention to treat analysis at 96 weeks (noncomplete equals failure), the atazanavir/r and lopinavir/r arms had similar proportions of patients with HIV RNA suppression to less than 50 copies/ml – 33 and 36% ($p > 0.01$), respectively. They also experienced similar median increases in CD4 cell count of 160 and 142 cells/μl. In the subgroup of patients with less than four PI mutations at baseline, there was a difference in virologic suppression of less than 50 copies/ml between the atazanavir/r arm (39%) and the lopinavir/r arm (46%). For patients with four or more PI mutations, both atazanavir/r and lopinavir/r performed poorly with virologic suppression to less than 50 copies/ml in only 20 and 23% of patients, respectively. Additionally, in the ANRS Puzzle 2 study, an atazanavir/r-based regimen had minimal virologic activity in patients with extensive treatment experience and many PI mutations [80]. The results of the BMS AI424–045 and ANRS Puzzle 2 studies clearly show the limited utility of atazanavir/r in the treatment of ART-experienced patients with multidrug-resistant virus. In addition, as will be discussed later, emergence of a unique PI-resistance mutation to atazanavir/r increases susceptibility to subsequent PIs. For these reasons, we recommend atazanavir/r-based ART primarily for first or second (first PI-class) line HIV treatment.

Novel strategies & regimens

Recently, studies evaluated atazanavir/r in new strategies or combinations with novel classes of antiretrovirals. The rationale behind these new approaches was to minimize long-term toxicity and improve the durability of life-long therapy. Two studies were open-label, prospective, single-arm pilot trials of regimen simplification to atazanavir/r alone after achieving virologic suppression for at least 1 year [81,82]. In ACTG 5201, among the 34 patients enrolled, only four (12%) had virologic failure 48 weeks after simplification to only atazanavir/r [81]. None of the patients developed major genotypic resistance by standard or single-genome sequencing assays. In addition, patients with virologic failure were more likely to have study visits with undetectable atazanavir concentrations, strongly suggesting that suboptimal adherence, not resistance, was the reason for virologic failure. Another study of ART simplification to atazanavir/r monotherapy was terminated early owing to virologic failure in five (33%) of the first 15 patients enrolled [82]. In this study, plasma atazanavir concentrations were not associated with virologic failure; however, patients with virologic failure were noted to have significantly lower median serum bilirubin concentrations. Once again, there was no evidence of major genotypic resistance to PIs in patients with virologic failure. Until this strategy can be tested in larger randomized clinical trials, it is not recommended to simplify cART to atazanavir/r monotherapy.

The Atazanavir and Lamivudine Simplification (ATLAS) study tested a simplification strategy aimed at limiting NRTI-associated toxicity. Investigators switched patients with optimal virologic control on atazanavir/r plus two NRTIs to atazanavir/r plus lamivudine [83]. Of 40 enrolled patients, 39 discontinued tenofovir and one abacavir. At the time of preliminary analysis and presentation, 34 patients had reached week 24 and they all maintained HIV RNA suppression to less than 50 copies/ml on the atazanavir/r plus lamivudine regimen. The investigators also observed an increase in lipids that did not negatively affect the cholesterol:high-density lipoprotein (HDL) ratio and improved renal function (Cockroft–Gault: +5 ml/min; $p = 0.004$). Again, it is too early to speculate about

whether or not this will be a safe, durable and worthwhile simplification strategy with atazanavir/r.

As a strategy to reduce long-term toxicities from ritonavir, the Atazanavir Ritonavir Induction with Epzicom Study (ARIES) enrolled ART-naive patients and administered abacavir/lamivudine plus atazanavir/r followed by randomization at week 36 for those with successful virologic suppression to maintain or discontinue low-dose ritonavir [75]. A total of 48 weeks after randomization, atazanavir was found to be noninferior to atazanavir/r (95% CI around the treatment difference: −1.75–12.48%) with 181 of 210 patients (86%) in the atazanavir group and 169 of 209 in the atazanavir/r group (81%) maintaining a HIV RNA level below 50 copies/ml. Notably, during simplification, the unboosted atazanavir group had fewer grade 2–4 adverse events (mainly hyperbilirubinemia) and improved fasting lipid measurements. In particular, significant differences in median levels of total cholesterol (173 vs 189 mg/dl; $p < 0.01$), low-density lipoprotein (LDL)-cholesterol (95 vs 102 mg/dl; $p < 0.01$) and triglycerides (123 vs 153 mg/dl) were reported after 48 weeks for unboosted atazanavir compared with atazanavir/r, respectively.

Atazanavir/r has also been studied in combination with maraviroc, a CCR5 inhibitor, as a once daily NRTI-sparing regimen. In the A4001078 study, investigators randomized 121 ART-naive patients to treatment with atazanavir/r plus maraviroc or the standard regimen of atazanavir/r plus tenofovir/emtricitabine [84]. Planned interim analyses at week 24 showed no statistical difference in virologic efficacy between the two arms, regardless of baseline HIV RNA. However, overall suppression of HIV RNA to less than 50 copies/ml was lower in the maraviroc arm (80 compared with 89%, for maraviroc vs tenofovir/emtricitabine, respectively). Interestingly, the difference between the two groups was greatest for those with baseline HIV RNA of less than 100,000 copies/ml, where HIV RNA suppression to less than 50 copies/ml was achieved in 80% of patients in the maraviroc arm and 95% in the tenofovir/emtricitabine arm. Again, these differences were not statistically significant in this preliminary interim analysis and we await analyses of the primary week-48 end point.

In the Safety and Potency of Atazanavir and Raltegravir Treatment in Absence of Nucleosides and Ritonavir (SPARTAN) study, 94 ART-naive patients were randomized 2:1 to unboosted atazanavir plus raltegravir (both dosed twice daily) or the standard regimen of atazanavir/r plus tenofovir/emtricitabine [85]. In a modified intention to treat analysis, 75% of patients in the atazanavir plus raltegravir arm and 63% of patients in the atazanavir/r plus tenofovir/emtricitabine arm reached HIV RNA levels of less than 50 copies/ml at week 24. A total of six patients in the atazanavir plus raltegravir arm and one patient in the atazanavir/r plus tenofovir/emtricitabine arm were evaluable for genotypic resistance testing (HIV RNA level greater than 400 copies/ml). None of the patients in either arm experienced atazanavir resistance; however, four of the six patients on raltegravir had acquired genotypic or phenotypic resistance to this agent. The investigators also reported grade 4 bilirubin elevations in 21% of patients on atazanavir plus raltegravir compared with 0% on atazanavir/r plus tenofovir/emtricitabine. At this interim week-24 analysis, the difference in HIV RNA suppression was not statistically different between the two arms, but the trial has been terminated owing to the unacceptably high rate of resistance and grade 4 bilirubin elevation in the atazanavir plus raltegravir arm.

Resistance

Atazanavir/r has a high barrier to genotypic resistance, and when resistance does emerge, it has a favorable and unique resistance pattern compared with other PIs. In all the clinical trials reviewed and summarized in Table 3, during the first 48–96 weeks of atazanavir/r-based cART, major genotypic PI mutations emerged in only four patients. As noted in several prior reviews on atazanavir, substitution of isoleucine to leucine at residue 50 (I50L)

of the HIV protease enzyme is the signature major genotypic resistance mutation that emerges in patients on atazanavir with virologic failure [86,87]. In one study, the investigators analyzed clinical isolates from patients enrolled in three clinical trials of atazanavir [86]. Among 208 patients with virologic failure, they identified 14 (7%) isolates with phenotypic resistance to atazanavir. After genotypic analysis, all of these isolates had the I50L substitution and resistance was specific for atazanavir. Notably, isolates with the I50L mutation had increased susceptibilities to other PIs such as lopinavir and nelfinavir. Another report showed that the I50L substitution induced atazanavir resistance and increased susceptibility to other PIs at the level of protease enzyme inhibition [87]. The I50L substitution increased PI susceptibility even in the presence of other primary and secondary PI-resistance substitutions. Based on these findings, the authors concluded that the I50L substitution likely causes a conformational change in protease that exploits a unique structural feature of atazanavir resulting in its reduced binding to protease; however, the enzyme active site in turn becomes more accessible to other inhibitors. The clinical applicability of this is not entirely clear, but these findings suggest that optimal sequencing of PI-based regimens, starting with atazanavir/r, may lead to greater durability and long-term success of cART.

Safety & tolerability

In general, cART regimens containing atazanavir/r have excellent tolerability and safety. The safety and tolerability data from Phase II and III clinical trials has been summarized in Table 4 [64,67–69,71–73,75,76,79,84,88]. Only 1–8% of patients in these studies discontinued treatment owing to medication-related toxicity. Approximately 20–60% experienced grade 2 or higher clinical or laboratory adverse events. The most common events were hyperbilirubinemia, jaundice and nausea. Less frequently noted were scleral icterus, diarrhea and rash. Compared with other boosted PI regimens, atazanavir/r has better gastrointestinal tolerance with significantly less nausea and diarrhea [69,71–73]. In the ARTEN study, patients on atazanavir/r-based cART had a lower frequency of rash and fewer discontinuations due to rash compared with patients on a nevirapine-based regimen [79]. Finally, as expected, patients on efavirenz-based cART experienced more CNS toxicity compared with those on atazanavir/r [76].

Hyperbilirubinemia

As previously mentioned, common clinical side effects of atazanavir/r are scleral icterus and jaundice as a consequence of hyperbilirubinemia. Elevated total bilirubin was found to be the most common laboratory abnormality in clinical trials investigating atazanavir with and without ritonavir boosting [59]. Abnormality occurred in over 80% of patients with 30–60% experiencing grade 3 or 4 elevations and 5–10% developing clinical jaundice or scleral icterus. Despite the frequent occurrence of this laboratory abnormality, study patients infrequently (<5%) discontinued atazanavir/r owing to this problem. The mechanism of this laboratory elevation is atazanavir-mediated inhibition of microsomal enzyme UGT 1A1, which results in elevated levels of unconjugated bilirubin [89,90]. Reduced activity of this enzyme has also been noted in 3–10% of the general population who have Gilbert syndrome, the most common inherited cause of unconjugated hyperbilirubinemia, due to a polymorphism in the gene encoding UGT1A1 [89]. In a study of 96 HIV-infected patients, 67% of individuals who were homozygous for *UGT1A1*28* and receiving atazanavir (or indinavir) had at least two episodes of hyperbilirubinemia in the clinical jaundice range compared with only 7% of those with the allele and not on atazanavir [89]. If a patient expressed concern over the possibility of developing jaundice while on atazanavir/r, testing for the presence of the *UGT1A1*28* genotype might be considered; however, the clinical utility of this approach has not been adequately studied.

While the physical appearance of having jaundice or scleral icterus can be distressing to some patients, atazanavir-induced hyperbilirubinemia has no other known adverse short or long-term consequences. In clinical studies, this phenomenon was not associated with signs, symptoms or laboratory evidence of hepatocellular injury and it should not be considered a PI-related hepatotoxicity. Grade 3 or 4 aspartate aminotransferase or alanine aminotransferase elevations occurred in less than 10% of patients on atazanavir/r and there has been no evidence of acute or progressive liver disease, even among those with viral hepatitis co-infection [39,57,64,69,72,91–93]. Of note, patients co-infected with HIV and HCV receiving atazanavir-based cART had a greater frequency of bilirubin elevation and jaundice during PEGylated-interferon and ribavirin treatment of HCV compared with those on cART regimens without atazanavir [94].

In the only head-to-head randomized clinical trial comparing atazanavir/r- and unboosted atazanavir-based regimens, pharmacologic boosting with ritonavir increased the frequency of total bilirubin elevation (greater than 2.5 times the normal upper limit in 60 vs 20%, respectively) and clinical jaundice (3 vs <1%, respectively) [64]. An equal number of participants in each arm experienced grade 3 or 4 total bilirubin and alanine amino-transferase or aspartate aminotransferase elevation (3 vs 3%, respectively). Discontinuation of therapy owing to hyperbilirubinemia was numerically higher in those on atazanavir/r (4 vs <1%), but this difference did not reach statistical significance.

If bilirubin elevation or clinical jaundice becomes problematic for a patient on atazanavir/r, then simplification to unboosted atazanavir might be a simple solution for selected patients. There is evidence to suggest that the total bilirubin level positively correlates with systemic atazanavir concentrations [75,95,96]. In two simplification studies, total bilirubin declined after removal of ritonavir without sacrificing virologic suppression and efficacy. The subset of patients with clinical symptoms of hyperbilirubinemia was not separately analyzed; however, one might expect them to have higher levels of atazanavir and more success with this strategy. At the current time, we would consider simplification from atazanavir/r to atazanavir as an option only for patients on their first PI-based cART regimen with virologic suppression to a HIV RNA level below 50 copies/ml and severe hyperbilirubinemia leading to noticeable clinical jaundice.

Nephrolithiasis

A rare side effect reported in patients receiving atazanavir that HIV providers should be aware of is nephrolithiasis [97–100]. Several case reports [97,99,100] and a review of the FDA's adverse event reporting system [98] identified this problem several years ago. In the FDA report, from December 2002 to January 2007, there were 30 cases of nephrolithiasis in HIV-infected patients taking atazanavir-based cART. Among the 20 cases reporting complete cART information, 13 patients were receiving concomitant tenofovir and 17 patients were receiving atazanavir boosted with low-dose ritonavir. Atazanavir was detected, by infrared spectrophotometry, in kidney stones of 12 of 14 cases undergoing stone analysis. There was considerable morbidity, with 18 (60%) patients requiring hospitalization, seven (23%) patients receiving outpatient care and eight (27%) patients requiring interventions of lithotripsy, ureteral stent insertion, endoscopic stone extraction or nephrostomy study placement. A total of five patients (17%) developed elevation in serum creatinine, suggestive of acute renal insufficiency. Renal function normalized after stone removal and atazanavir discontinuation in all patients except one with baseline chronic renal disease. Owing to the small number of cases, risk factors for atazanavir-induced nephrolithiasis are not known. Therefore, there is uncertainty as to whether or not increased atazanavir drug levels or prolonged use are associated with this adverse condition. Nephrolithiasis is a well-known adverse effect associated with indinavir therapy, with a reported frequency of approximately 12% [101]. Like indinavir, atazanavir has pH-dependent solubility (optimal

pH: 1.9), and may crystallize in a basic environment. It is unclear if strategies to maintain high urinary output or achieve urine acidification are safe or effective in preventing atazanavir-associated nephrolithiasis. HIV providers prescribing cART with atazanavir/r should be aware of the possibility of nephrolithiasis and if signs or symptoms of this problem occur, one should consider discontinuation of atazanavir and substitution with an appropriate alternative agent.

Lipid elevations

Over the past several years, one of the major issues in HIV management has been the development of metabolic disturbances, including hyperlipidemia, and the potential for increasing cardiovascular disease risk. Nearly all HIV-infected patients experience increases in lipid levels on cART, but they have been most pronounced among patients treated with PIs until the introduction of atazanavir. Clinical trials of atazanavir/r and its effects on lipids in comparison with other medications are summarized in Table 5. Summarizing these studies, after 48 weeks of atazanavir/r-based cART, total cholesterol levels increased from 15 to 31 mg/l, LDL increased from 4 to 22 mg/dl, HDL increased from 4 to 11 mg/dl and triglycerides increased from 7 to 34 mg/dl [64,69,71–74,76,79]. In comparative studies with other boosted PIs (fosamprenavir/r and lopinavir/r) (Table 5), atazanavir/r had consistently lower elevations in nearly all lipid levels by week 48 [69,71–73]. The greatest differences were in triglycerides and total cholesterol. In the ACTG 5202 study, at 96 weeks, patients treated with atazanavir/r had significantly lower increases in fasting total cholesterol, LDL and HDL compared with efavirenz, regardless of the NRTI backbone used [76]. Several other studies have switched patients with suppressed HIV RNA from other PI-based cART regimens to atazanavir/r, with subsequent improvements observed in lipids (Table 5) [102–107]. Using this strategy, the total cholesterol decreased from 12 to 25 mg/dl, LDL decreased from 4 to 6 mg/dl and triglycerides decreased from 38 to 182 mg/dl, depending on the population studied. In the Switch to Atazanavir and Brachial Artery (SABAR) study, lipids improved, but there was no observed change in brachial artery reactivity among those who switched to atazanavir/r compared with those who stayed on a different boosted PI [102]. After 48 weeks of simplification of atazanavir/r to unboosted atazanavir in the ARIES, the median increases of total cholesterol, LDL and triglycerides were 16, 7 and 30 mg/dl lower, respectively, compared with patients remaining on atazanavir/r [75]. This suggests that low-dose ritonavir or its pharmacologic boosting effect on atazanavir results in a smaller lipid increase over time, and that simplification to atazanavir, if viremia is suppressed, might be a viable strategy for patients with elevated lipids or high cardiovascular risk on atazanavir/r-based regimens [75,108].

Preliminary studies comparing the newest PI, darunavir, to atazanavir (both with ritonavir boosting) have not shown any significant differences in lipid changes [109,110]. Long-term follow-up and results of METABOLIK, ACTG 5257 and its metabolic substudy (ACTG 5260) are awaited to appropriately evaluate the metabolic differences between these two PIs. METABOLIK is a 48-week, Phase IV, multicenter study comparing changes in lipids, insulin sensitivity and inflammatory biomarkers among patients randomized to either atazanavir/r or darunavir/r. ACTG 5257 is an ongoing Phase III clinical trial of ART-naive patients randomized to atazanavir/r-, darunavir/r-, or raltegravir-based regimens for initial cART.

Significant elevations in lipids are associated with an increase in 10-year cardiovascular disease risk; however, it is unclear exactly how HIV infection or cART alters this risk. Nevertheless, cardiovascular disease has become a growing problem for the aging HIV-infected population, and clinicians should provide patients with the best therapies aimed at minimizing both short-term toxicity and long-term comorbidities. We await future results

from the D:A:D cohort regarding the impact of atazanavir/r and other PIs on the risk of cardiovascular disease.

Fat & glucose metabolism

Several studies have evaluated the effects of atazanavir/r on fat and glucose metabolism. Compared with unboosted atazanavir, after 96 weeks of treatment, patients treated with atazanavir/r-based cART had no significant difference in increases in total or subcutaneous adipose tissue measured by computed tomography and dual-energy X-ray absorptiometry [111]. In a study of patients who switched from lopinavir/r to atazanavir/r, 6 months after this change, there was a significant increase in glucose uptake by muscle, decreased visceral adipose tissue and decreased fasting glucose [106]. Another small study of patients who switched from a PI-based regimen to atazanavir/r reported an improvement in insulin sensitivity 3 months after the change [112]. A third study comparing HIV-negative healthy volunteers on lopinavir/r and atazanavir/r found that those on atazanavir/r had less glucose uptake inhibition *in vitro* and lopinavir/r led to detectable insulin resistance *in vivo* [113]. These results suggest that patients treated with atazanavir/r may have less long-term metabolic toxicity with decreased incidence of metabolic syndrome and diabetes compared with those treated with other PIs. Further studies are required before conclusions or recommendations can be made based on these clinical end points.

Conclusion

Since the introduction of cART in 1996, anti-retroviral therapy options for the treatment of HIV infection have become simpler, less toxic and more potent. Current International AIDS Society recommendations for the treatment of HIV-1 infection in adults include two NRTIs plus either efavirenz, ritonavir-boosted atazanavir or darunavir, or raltegravir [3]. As a preferred antiretroviral agent, atazanavir/r has been extensively studied and widely prescribed throughout the USA and Europe. Currently, atazanavir/r is a preferred boosted PI for initial cART owing to its excellent pharmacokinetic properties, ease of dosing, virologic potency, minimal toxicity (including lipid elevations), high genetic barrier to resistance and favorable resistance profile in the setting of virologic failure. Important potential limitations of cART with atazanavir/r are interactions with acid-reducing agents and those mediated by low-dose ritonavir, the development of severe hyperbilirubinemia with clinical jaundice and a rare risk of nephrolithiasis. Strategies using atazanavir/r in novel regimens, including combinations with CCR5 inhibitors, require further investigation, but may provide less-toxic NRTI-sparing options in the near future. The ongoing METABOLIK and ACTG 5257 randomized clinical trials will assess differences in efficacy and safety between atazanavir/r and darunavir/r for first-line boosted PI-based cART. At least until then, atazanavir/r will continue to be a widely prescribed drug in the PI class for the treatment of HIV infection.

Future perspective

In the next 10 years, atazanavir/r will continue to be a vital part of cART for the treatment of HIV infection. We foresee cART regimens becoming even simpler, more potent and less toxic. Excellent pharmacokinetic properties, virologic durability and less metabolic toxicity will make atazanavir/r an important part of new NRTI-sparing regimens with CCR5 inhibitors, integrase inhibitors and other novel antiretroviral agents. Additionally, co-formulation of atazanavir and low-dose ritonavir in a heat-stable tablet, currently being developed for use in resource-limited settings, will significantly increase worldwide uptake of this drug. We foresee that the earlier control of HIV replication could improve comorbidities, such as cardiovascular disease, related to inflammation as well as PI-based cART. We should continuously aim to provide all HIV-infected patients worldwide with the best treatment options possible.

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Executive summary

Mechanism of action

- Atazanavir is an azapeptide HIV-1 protease inhibitor (PI) that prevents the formation of mature virions through the potent and selective inhibition of viral Gag and Gag–Pol polyprotein processing in HIV-1-infected cells.

Pharmacokinetics

- Following oral administration with low-dose ritonavir, atazanavir is rapidly absorbed into the systemic circulation, reaching its peak concentration in approximately 3 h and steady-state concentration after 4–8 days.
- Atazanavir dissolution and absorption are highly dependent on gastric pH.
- Atazanavir should always be administered with food to improve absorption and reduce variability.
- Atazanavir is highly protein-bound in serum to α-1-acid glycoprotein and albumin.
- Estimated atazanavir cerebrospinal fluid (CSF) penetration is 0.74% of plasma concentration, which may not consistently provide effective antiviral activity in the CSF. The CNS penetration-effectiveness score proposed by the CHARTER Study Group is 2.
- Similar to other protease inhibitors, atazanavir is extensively metabolized in the liver, primarily by cytochrome (CYP450)3A isoenzymes – 3A4 and 3A5.

Drug interactions

- Tenofovir decreases the atazanavir area under the plasma concentration–time curve and C_{min} by 25 and 40%, respectively. When boosted with low-dose ritonavir, the interaction is largely overcome.
- Tenofovir should only be given with boosted atazanavir.
- Co-administration of atazanavir with acid-suppressing agents, such as proton pump inhibitors or H_2-receptor antagonists, results in a decrease in atazanavir plasma concentrations.
- Recommendations for use of atazanavir pharmacologically boosted with ritonavir (atazanavir/r) with acid-suppressing agents are reviewed in Table 2.

Clinical efficacy & resistance

- Atazanavir administered with low-dose ritonavir (atazanavir/r)-based combination antiretroviral therapy (cART) has demonstrated greater virologic efficacy and less development of resistance compared with unboosted atazanavir.
- Overall, atazanavir/r-based cART is highly efficacious, with virologic suppression to less than 50 copies/ml achieved in 75–84% of ART-naive patients and 33% of ART-experienced patients.
- Compared with other boosted PI-based regimens, atazanavir/r has equivalent virologic efficacy and potentially better durability at 96 weeks.
- Virologic efficacy is also similar between atazanavir/r and non-nucleoside reverse transcriptase inhibitor (efavirenz and nevirapine)-based cART.

- Studies of non-nucleoside reverse transcriptase inhibitor-sparing regimens including atazanavir/r are ongoing. Preliminary results of a regimen of atazanavir/r plus maraviroc are encouraging; however, a study of unboosted atazanavir plus raltegravir (both given twice daily) was terminated at week 24 owing to an unacceptably high rate of resistance and grade 4 bilirubin elevation.
- Atazanavir/r has a high barrier to genotypic resistance and, when resistance does emerge, it has a favorable and unique resistance pattern compared with other PIs.
- Optimal sequencing of PI-based regimens, starting with atazanavir/r, may lead to greater durability and long-term success of cART.

Safety & tolerability

- cART regimens containing atazanavir/r have excellent safety and tolerability.
- The most common adverse events are hyperbilirubinemia, jaundice and nausea.
- Grade 3 or 4 elevation in total bilirubin due to inhibition of microsomal enzyme uridine-glucuronosyl transferase 1A1 occurs in 30–60% of patients on atazanavir/r with 5–10% experiencing clinical jaundice or scleral icterus.
- Atazanavir-induced hyperbilirubinemia has no known adverse short- or long-term consequences and patients infrequently (<5%) discontinue therapy for this reason.
- A rare, but potentially morbid, side effect of atazanavir is nephrolithiasis.
- Compared with other boosted PIs, atazanavir/r has less hyperlipidemia and better gastrointestinal tolerance.
- Compared with nevirapine, atazanavir/r has a lower frequency of rash, and compared with efavirenz, it has lower CNS toxicity and causes less hyperlipidemia.

Table 1

Steady-state pharmacokinetics of atazanavir in HIV-infected patients in a fed state.

Dosage	C_{max} in ng/ml (%)	C_{min} † in ng/ml (%)	Half-life in hours (%)	AUC in ng-h/ml (%)
Atazanavir 400 mg once daily	2298 (71)	120 (109)	6.5 (2.6)	14,874 (91)
Atazanavir 300 mg + ritonavir 100 mg once daily	4422 (58)	636 (97)	8.6 (2.3)	46,073 (66)

All values not in parentheses are the geometric mean. The percentage values are the coefficient of variation.

†Recommended therapeutic target for optimal virologic suppression, C_{min} >150 ng/ml [114].

AUC: Area under the plasma concentration–time curve; C_{max}: Maximum (peak) plasma concentration; C_{min}: Minimum (trough) plasma concentration.

Table 2

Recommendations for the use of atazanavir/ritonavir[†] with acid-suppressing agents.

	H_2-receptor antagonists		Proton pump inhibitors	
	Treatment-naive patients	***Treatment-experienced patients***	***Treatment-naive patients***	***Treatment-experienced patients***
Without tenofovir	Do not exceed dose equivalent of famotidine 40 mg twice daily[‡]	Do not exceed dose equivalent of famotidine 20 mg twice daily[‡]	Do not exceed dose equivalent of omeprazole 20 mg once daily[§] Consider an increase to atazanavir/r 400/100 mg once daily	Co-administration should be avoided
With tenofovir	Do not exceed dose equivalent of famotidine 40 mg twice daily[‡]	Do not exceed dose equivalent of famotidine 20 mg twice daily[‡] Increase atazanavir/r to 400/100 mg once daily	Do not exceed dose equivalent of omeprazole 20 mg once daily[§] Consider an increase to atazanavir/r 400/100 mg once daily	Co-administration should be avoided

[†]Except where noted, atazanavir should be given as 300 mg with ritonavir 100 mg once daily.

[‡]Atazanavir/r should be administered simultaneously with or at least 10 h after the H_2-receptor antagonist.

[§]Omeprazole should be administered approximately 12 h prior to atazanavir/r.

Atazanavir/r: Atazanavir/ritonavir.

Table 3

Summary of atazanavir/ritonavir efficacy in clinical trials.

Study	Phase	Patient type (n)	HIV RNA <50 copies/ml (%)	Increase in $CD4^+$ count (cells/μl)	Emergence of major genotypic resistance (n)	Discontinuation (%)	Follow-up (weeks)	Ref.
BATON	II	Naive (102)	81	+217	0	17	48	[67]
COL102060	II	Naive (112)	77	+188	1	14	48	[68]
ARIES	III	Naive (515)	80	+171	0	14	36	[74]
BMS AI424–089	III	Naive (200)	ATV/r: 75 ATV: 70	ATV/r: +174 ATV: +213	ATV/r: 0 ATV: 3	ATV/r: 12 ATV: 10	48	[64]
ACTG 5202	III	Naive (1867)	NR (see text for virologic end point)	ATV/r + TDF/FTC: +252 EFV + TDF/FTC: +221	Greater emergence for EFV compared with ATV/r Numbers not reported	NR	96	[76]
ARTEN	III	Naive (569)	ATV/r: 74 NVP: 70	ATV/r: +185 NVP: +170	NR	ATV/r: 9 NVP: 25	48	[79]
ALERT	III	Naive (106)	ATV/r: 83 FPV/r: 75	ATV/r: +183 FPV/r: +170	NR	ATV/r: 8 FPV/r: 15	48	[73]
CASTLE (results from week 48)	III	Naive (883)	ATV/r: 78 LPV/r: 76	ATV/r: +203 LPV/r: +219	ATV/r: 1 LPV/r: 0	ATV/r: 9 LPV/r: 13	48	[72]
CASTLE (results from week 96)	III	Naive (883)	ATV/r: 74 LPV/r: 68	ATV/r: +268 LPV/r: +290	ATV/r: 2 LPV/r: 1	ATV/r: 16 LPV/r: 22	96	[72]
BMS AI424–045	III	Exp. (243)	ATV/r: 33 LPV/r: 36	ATV/r: +160 LPV/r: +142	NR	ATV/r: 44 LPV/r: 47	96	[69]
A4001078	II	Naive (121)	MVC: 80 TDF/FTC: 89	MVC: +195 TDF/FTC: +173	NR	MVC: 8 TDF/FTC: 7	24	[84]

ALERT: Atazanavir or Lexiva with Ritonavir and Truvada; ARIES: Atazanavir Ritonavir Induction with Epzicom Study; ARTEN: Atazanavir/Ritonavir on a Background of Tenofovir and Emtricitabine (Truvada) Versus Nevirapine; ATV/r: Atazanavir/ritonavir; BATON: Boosted Atazanavir and Truvada Given Once-Daily; BMS: Bristol-Myers Squibb; CASTLE: Comparison of Atazanavir/Ritonavir in Naive Subjects in Combination with Tenofovir/Emtricitabine Versus Lopinavir/Ritonavir in Combination with Tenofovir/Emtricitabine to Assess Safety and Efficacy; EFV: Efavirenz; Exp.: ART-experienced; FPV/r: Fosamprenavir/ritonavir; LPV/r: Lopinavir/ritonavir; MVC: Maraviroc; Naive: ART-naive; NR: Not reported; NVP: Nevirapine; TDF/FTC: Tenofovir/emtricitabine.

Table 4

Summary of atazanavir/ritonavir safety and tolerability in clinical trials.

Study	Most common adverse events	Discontinued owing to any adverse event (%)	Ref.
BATON	Diarrhea, nausea, scleral icterus	6	[67]
COL102060	Hyperbilirubinemia, icterus, jaundice	3	[68]
ARIES	Hyperbilirubinemia, diarrhea, nausea	3	[74]
BMS AI424–089	Jaundice, headache, rash	ATV/r: 8 ATV: <1	[64]
ACTG 5202	General body complaints and cholesterol elevations	No difference between ATV/r and EFV Numbers not reported	[76]
ARTEN	ATV/r: hyperbilirubinemia NVP: rash	ATV/r: 4 NVP: 14	[79]
ALERT	ATV/r: hyperbilirubinemia, diarrhea, nausea FPV/r: diarrhea, nausea, rash	ATV/r: 1 FPV/r: 1	[73]
CASTLE	ATV/r: jaundice, nausea, rash LPV/r: diarrhea, nausea, rash	ATV/r: 3 LPV/r: 5	[72]
BMS AI424–045	ATV/r: jaundice, nausea, scleral icterus LPV/r: diarrhea, nausea, lipodystrophy	ATV/r: 8 LPV/r: 8	[69]
A4001078	Jaundice, hyperbilirubinemia, nausea	MVC: 3 TDF/FTC: 0	[84]

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Table 5

Summary of lipid alterations among patients on atazanavir/ritonavir in clinical trials.

Study	Intervention type	Patient type (n)	Lipid changes (%)[†]	Follow-up (weeks)	Ref.
ARIES	Single arm (ATV/r + ABC/3TC)	Naive (515)	TC increase: 31 LDL increase: 11 HDL increase: 10 TG increase: 34	36	[74]
BMS AI424–089	Comparison (ATV/r vs ATV)	Naive (200)	ATV/r: TC increase: 24 LDL increase: 22 HDL increase: 9 TG increase: 14 ATV: TC increase: 11 LDL increase: 16 HDL increase: 9 TG decrease: 15	48	[64]
ACTG 5202	Comparison (ATV/r vs EFV)	Naive (1867)	EFV consistently associated with significantly greater increase in fasting TC, LDL, and HDL compared with ATV/r regardless of NRTI backbone used TG also when paired with ABC/3TC Numbers not reported	96	[76]
ARTEN	Comparison (ATV/r vs NVP)	Naive (569)	ATV/r: TC increase: 20 LDL increase: 11 HDL increase: 4 TG increase: 28 NVP: TC increase: 24 LDL increase: 15 HDL increase: 10 TG decrease: 0.2	48	[79]
ALERT	Comparison (ATV/r vs FPV/r)	Naive (106)	ATV/r: TC increase: 15 LDL increase: 4 HDL increase: 11 TG increase: 7 FPV/r: TC increase: 11 LDL increase: 4 HDL increase: 5 TG increase: 34	48	[73]
CASTLE	Comparison (ATV/r vs LPV/r)	Naive (883)	ATV/r:	48	[71]

Study	Intervention type	Patient type (n)	Lipid changes (%)†	Follow-up (weeks)	Ref.
			TC increase: 12 LDL increase: 12 HDL increase: 27 TG increase: 13 LPV/r: TC increase: 24 LDL increase: 15 HDL increase: 32 TG increase: 51		
BMS AI424–045	Comparison (ATV/r vs LPV/r)	Exp. (443)	ATV/r: TC decrease: 7 LDL decrease: 11 TG decrease: 2 LPV/r: TC increase: 9 LDL increase: 1 TG increase: 30	96	[69]
Stanley *et al.*	Switch (LPV/r to ATV/r)	Hyperinsulinemia, and/or dyslipidemia, virologically suppressed (15)	TC decrease: 23 TG decrease: 182	24	[106]
ATAZIP	Switch (LPV/r to ATV/r)	Virologically suppressed (248)	TC decrease: 24 TG decrease: 53	96	[104]
SWAN	Switch (any PI to ATV or ATV/r)	Virologically suppressed (419)	Switch: TC decrease: 15 LDL decrease: 12 Non-HDL decrease:18 TG decrease: 33 No switch: TC decrease: 3 LDL decrease: 5 Non-HDL decrease: 3 TG increase: 9	48	[103]
Calza *et al.*	Switch (any PI to ATV/r)	Hyperlipidemia and virologically suppressed (89)	TG decrease: 15 TC decrease: 16 LDL decrease: 18	48	[107]
SLOAT	Switch (LPV/r to ATV/r or ATV)	Virologically suppressed (189)	Switch: TC decrease: 12 LDL increase: 4 HDL increase: 2 TG decrease: 38 No Switch:	48	[105]

Study	Intervention type	Patient type (n)	Lipid changes (%)†	Follow-up (weeks)	Ref.
			TC decrease: 0.5 LDL decrease: 0.5 HDL increase: 1 TG decrease: 5		
SABAR	Switch (any boosted PI to ATZ/r)	Hyperlipidemia and virologically suppressed (50)	Switch: TC decrease: 25 LDL decrease: 6 TG decrease: 58 No Switch: TC increase: 2 LDL increase: 4 TG increase: 4	24	[102]

†Mean change in mg/dl unless otherwise noted.

ABC/3TC: Abacavir/lamivudine; ALERT: Atazanavir or Lexiva with Ritonavir and Truvada; ARIES: Atazanavir Ritonavir Induction with Epzicom Study; ARTEN: Atazanavir/Ritonavir on a Background of Tenofovir and Emtricitabine (Truvada) Versus Nevirapine; ATV: Atazanavir; ATV/r: Atazanavir/ritonavir; BMS: Bristol-Myers Squibb; CASTLE: Comparison of Atazanavir/Ritonavir in Naive Subjects in Combination with Tenofovir/Emtricitabine Versus Lopinavir/Ritonavir in Combination with Tenofovir/Emtricitabine to Assess Safety and Efficacy; EFV: Efavirenz; Exp: ART-experienced; FPV/r: Fosamprenavir/r; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LPV/r: Lopinavir/r; Naive: ART-Naive; NRTI: Nucleoside reverse transcriptase inhibitors; NVP: Nevirapine; PI: Protease inhibitor; SABAR: Switch to Atazanavir and Brachial Artery Study; TC: Total cholesterol; TG: Triglycerides.