
# Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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# Atazanavir (ATV, Reyataz) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

## Formulations

**Capsules:** 100 mg, 150 mg, 200 mg, and 300 mg

## Dosing Recommendations

**Neonate/infant dose:**

- Not approved for use in neonates/infants. ATV should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

**Pediatric dose:**

- Data are insufficient to recommend dosing in children aged <6 years.

**For children aged ≥6 to <18 years:**

| Weight (kg) | Once-Daily Dose |
|---|---|
| 15–<20 kg | ATV 150 mg + RTV 100 mg, both once daily with food |
| 20–<32 kg | ATV 200 mg + RTV 100 mg, both once daily with food |
| 32–<40 kg | ATV 250 mg* + RTV 100 mg, both once daily with food |
| ≥40 kg | ATV 300 mg + RTV 100 mg, both once daily with food |

* Dose in mg requires two different capsule strengths of ATV. Additional patient education should be considered to avoid dosing errors (see text for discussion).

- *For treatment-naive pediatric patients who do not tolerate ritonavir (RTV):* **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.** Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children aged <13 years. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see *Pediatric Use*).
- Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.

## Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular (AV) block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- Increased serum transaminases
- Hyperlipidemia (primarily with RTV boosting)

## Special Instructions

- Administer ATV with food to enhance absorption.
- Additional patient education should be considered to avoid dosing errors when prescribing ATV 250 mg because this dose requires 2 different capsule strengths of ATV.
- Because ATV can prolong the electrocardiogram (ECG) PR interval, use ATV with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, special dosing information is indicated (see Drug Interactions for recommendations on dosing ATV when the drug is co-administered with H2 receptor antagonists). When administered with buffered didanosine (ddI) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddI administration.



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**Adolescent (aged ≥18–21 years)/adult dose:**
*Antiretroviral-naive patients:*

- ATV 300 mg + RTV 100 mg or ATV 400 mg once daily with food (if unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels [see *Pediatric Use*]).

*Antiretroviral-experienced patients:*

- ATV 300 mg + RTV 100 mg, both once daily with food.

*ATV in combination with efavirenz (EFV) (adults) in therapy-naive patients only:*

- ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily at separate times.
- Although ATV/r should be taken with food, EFV should be taken on an empty stomach, preferably at bedtime. EFV should not be used with ATV (with or without RTV) in treatment-experienced patients because EFV decreases ATV exposure.

*ATV in combination with tenofovir (TDF) (adults):*

- ATV 300 mg + RTV 100 mg + TDF 300 mg, all once daily with food.
- Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is co-administered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive patients receiving PPIs should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted ATV. Co-administration of ATV with PPIs is not recommended in treatment-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients with marked elevations in transaminases before treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

## Metabolism

- ATV is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucoronosyltransferase (UGT1A1).
- Dosing of ATV in patients with hepatic impairment: ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
- Dosing of ATV in patients with renal impairment: No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

***Drug Interactions*** (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Atazanavir is both a substrate and an inhibitor of the cytochrome P (CYP) 3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucoronosyltransferase (UGT1A1). Atazanavir is a weak inhibitor of CYP2C8.
- A patient's medication profile should be carefully reviewed for potential drug interactions with atazanavir before the drug is administered.



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- *Nucleoside reverse transcriptase inhibitors (NRTIs):* Tenofovir decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be co-administered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be co-administered with atazanavir in treatment-experienced patients but may be used in combination with atazanavir 400 mg plus ritonavir boosting in treatment-naive adults.
- *Integrase Inhibitors:* Atazanavir is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir. This interaction may not be clinically significant.
- *Absorption:* Atazanavir absorption is dependent on low gastric pH. When atazanavir is administered with medications that alter gastric pH, dosage adjustment is indicated. No information is available on dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton-pump inhibitors (PPIs) in adults are as follows:

- *Antacids:* Atazanavir concentrations are decreased when the drug is co-administered with antacids and buffered medications (including buffered didanosine formulations); therefore, atazanavir should be administered 2 hours before or 1 hour after these medications.
- *H2-Receptor Antagonists (unboosted atazanavir in treatment-naive patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the antiretroviral (ARV) agent. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2 receptor antagonist (a single dose of an H2 receptor antagonist should not exceed a dose comparable to famotidine 20 mg; a total daily dose should not exceed a dose comparable to famotidine 40 mg).
- *H2-Receptor Antagonists (boosted atazanavir in treatment-naive or -experienced patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV. Dose recommendations for H2 receptor antagonists are either a ≤40-mg dose equivalent of famotidine twice daily for treatment-naive patients or a ≤20-mg dose equivalent of famotidine twice daily for treatment-experienced patients. Boosted atazanavir (ATV 300 mg + RTV 100 mg) should be administered simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist.
- *H2-Receptor Antagonists (boosted atazanavir with tenofovir):* Treatment-experienced patients using both tenofovir and H2-receptor antagonists should be given an increased dose of atazanavir (ATV 400 mg + RTV 100 mg + TDF 300 mg).
- *PPIs:* Coadministration of PPIs with atazanavir is expected to substantially decrease atazanavir plasma concentrations and decrease its therapeutic effect. Dose recommendations for therapy-naive patients are ≤20-mg dose equivalent of omeprazole taken approximately 12 hours before boosted atazanavir (ATV 300 mg + RTV 100 mg). Coadministration of atazanavir with PPIs is not recommended in treatment experienced patients.

***Major Toxicities:***

- *More common:* Indirect hyperbilirubinemia that can result in jaundice or icterus, but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias.
- *Less common:* Prolongation of PR interval of electrocardiogram. Abnormalities in atrioventricular (AV) conduction generally limited to first-degree AV block, but with rare reports of second-degree



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AV block. Rash, generally mild to moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other protease inhibitors (PIs). However, the addition of ritonavir to atazanavir is associated with lipid abnormalities but to a lesser extent than with other boosted PIs.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or hepatitis C are at increased risk).

***Resistance:*** The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ATV.html).

***Pediatric Use:*** Atazanavir is FDA-approved for use in children and adolescents. Ritonavir-boosted atazanavir is generally preferred over unboosted atazanavir and is used in combination with NRTIs for treatment in children aged ≥6 years.

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of ritonavir boosting, atazanavir can achieve protocol-defined pharmacokinetic (PK) targets, but only when used at higher doses of atazanavir (on a mg/kg body weight or mg/m$^2$ body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children older than 6 and younger than 13 years of age required atazanavir dosing of 520 mg/m$^2$ of body surface area per day of atazanavir capsule formulation to achieve PK targets. Doses required for older adolescents were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily: adolescents aged >13 years required atazanavir dosing of 620 mg/m$^2$ of body surface area per day.[1] In this study, the areas under the curve (AUCs) for the unboosted arms were similar to the ritonavir-boosted atazanavir groups but the maximum plasma concentration ($C_{max}$) was higher and minimum plasma concentration ($C_{min}$) lower for the unboosted arms. Median doses of atazanavir in mg/m$^2$ both with and without ritonavir boosting from IMPAACT/PACTG 1020A are outlined in the following table. When dosing unboosted atazanavir in pediatric patients, therapeutic drug monitoring (TDM) is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.[2] Higher target trough concentrations may be required in protease inhibitor (PI)-experienced patients.

**Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A[1]**

| Age range (years) | Was ATV given with RTV boosting? | ATV median dose (mg/m$^2$*) | ATV median dose (mg*) |
|---|---|---|---|
| 6–13 years | No | 509 | 475 |
| 6–13 years | Yes | 208 | 200 |
| >13 years | No | 620 | 900 |
| >13 years | Yes | 195 | 350 |

* Dose satisfied protocol-defined AUC/PK parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. TDM was used to determine patient-specific dosing in this trial.

Regarding toxicity, 8.5% (11 of 129) of patients enrolled in the trial had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram (ECG) abnormalities were observed in a small number of patients: Grade 3 QTC prolongation in 1 patient, Grade 2 PR or HR changes in 9 patients, and Grade 3 PR prolongations in 3 patients. No significant changes in serum cholesterol or triglycerides



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were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs.[3, 4]

A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A) supports the use of the following atazanavir/ritonavir doses: 150/100 mg (15–<20 kg), 200/100 mg (20–<40 kg), 300/100 mg (≥40 kg)[5] and the current FDA-approved product label recommends these weight-based doses. The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling.[5] The authors acknowledge that atazanavir/ritonavir at 250/100 mg appeared to be a more appropriate dose than atazanavir/ritonavir at 200/100 mg for the 35 to <40 kg weight group; however, this dose was not recommended in the product label because the 250 atazanavir dosage strength requires the use of 2 different capsule strengths and is prone to dosing errors.[5]

The doses of atazanavir/ritonavir recommended by the Pediatric ARV Guideline Panel are 200/100 mg for pediatric patients weighing 20 to <32 kg and 250/100 mg for patients weighing 32 to <40 kg while the FDA-approved dose of atazanavir/ritonavir is 200/100 mg for pediatric patients weighing 20 to <40 kg. The higher dose of 250/100 mg is recommended by the Pediatric ARV Guideline Panel at the 32 to <40 kg weight band to avoid underdosing. Additional patient education to prevent dosing errors is recommended when 250 mg of atazanavir is prescribed because this dosage requires the use of 2 different capsule strengths of atazanavir.

A population PK study of 51 children with mean age 14.3 years and weight 51 kg that targeted mean adult exposure for a 300/100 mg atazanavir/ritonavir dosage showed that the following atazanavir/ritonavir doses might be an appropriate alternative to the FDA recommendations: 200/100 (25–39 kg), 250/100 mg (39–50 kg) and 300/100 (>50 kg).[6] In addition, simulations suggested that the following doses should be used in children when combined with 300 mg tenofovir disoproxil fumarate (TDF): 250/100 mg for children weighing 35 to 39 kg, then 300/100 mg for children weighing over 39 kg.[6] The authors conclude that these recommendations should be prospectively confirmed.[6]

In a small, single-site study, 23 pediatric patients (median age 16 years) on combination antiretroviral therapy were switched to a once-daily ritonavir-boosted atazanavir-containing regimen because of virologic failure (12 patients) or for treatment simplification (11 patients).[7] Twenty of the patients had previously received PI-based regimens with the median number of two atazanavir-associated mutations acquired before switching to atazanavir/ritonavir. Patients received atazanavir doses lower than those currently recommended and many patients received concomitant therapy with tenofovir and/or didanosine. Both tenofovir and buffered didanosine have known drug interactions with atazanavir and can lower plasma concentrations. In this study, atazanavir plasma concentrations were measured at 12 to 15 hours after dosing: 6 patients had undetectable levels at multiple time points, and considerable interpatient variability in plasma atazanavir concentrations was noted. Four of the 13 patients who previously had undetectable viral loads experienced virologic failure; 6 of 12 patients who previously had virologic failure achieved undetectable viral loads.

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