Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Atazanavir (ATV, Reyataz) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Powder Packet: 50 mg/packet
Capsules: 150 mg, 200 mg, and 300 mg

Generic Formulations
Capsules: 150 mg, 200 mg, 300 mg

Fixed-Dose Combination Tablets:
- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg

Capsules and powder packets are not interchangeable.

Dosing Recommendations

Neonate Dose:
- Atazanavir is not approved for use in neonates and infants aged <3 months. Atazanavir should not be administered to neonates due to risks associated with hyperbilirubinemia (kernicterus).

Infant and Child Dose
Powder Formulation:
- The powder formulation must be administered with ritonavir.
- The powder formulation is not approved for use in infants aged <3 months or weighing <5 kg.

Atazanavir Powder Dosing Table for Infants and Children Aged ≥3 Months and Weighing ≥5 kg

<table>
<thead>
<tr>
<th>Weight</th>
<th>Once-Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg to &lt;15 kg</td>
<td>Atazanavir 200 mg (four packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food</td>
</tr>
<tr>
<td>15 kg to &lt;25 kgb</td>
<td>Atazanavir 250 mg (five packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food</td>
</tr>
</tbody>
</table>

Capsule Formulation:
- Capsules are not approved for use in children aged <6 years or weighing <15 kg.

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients
- Nephrolithiasis
- Increased serum transaminases
- Hyperlipidemia (occurs primarily with ritonavir boosting)

Special Instructions

- Administer atazanavir with food to enhance absorption.
- Capsules and powder packets are not interchangeable.
- Do not open capsules.
- Because atazanavir can prolong the PR interval, use atazanavir with caution in patients with pre-existing cardiac conduction system disease or with other drugs that are known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- Atazanavir absorption is dependent on low gastric pH; therefore, when atazanavir is administered with medications that alter gastric pH, dosing adjustments may be indicated (see the Drug Interactions section in the atazanavir package insert).
- The plasma concentration, and therefore the therapeutic effect, of atazanavir can be expected to decrease substantially when atazanavir is coadministered with proton-
Atazanavir Capsule Dosing Table for Children and Adolescents Aged ≥6 Years and Weighing ≥15 kg

<table>
<thead>
<tr>
<th>Weight</th>
<th>Once-Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 kg</td>
<td>Capsules not recommended</td>
</tr>
<tr>
<td>15 kg to &lt;35 kg</td>
<td>Atazanavir/ritonavir® 200 mg/100 mg, both once daily with food</td>
</tr>
<tr>
<td>≥35 kg</td>
<td>Atazanavir/ritonavir® 300 mg/100 mg, both once daily with food</td>
</tr>
</tbody>
</table>

For Treatment-Naive Children and Adolescents Who Do Not Tolerate Ritonavir:
- Atazanavir powder is not an option, since it must be administered with ritonavir. For the capsule formulation, while the Food and Drug Administration (FDA) does not recommend the use of unboosted atazanavir in children aged <13 years, adolescents aged ≥13 years weighing ≥40 kg may be prescribed unboosted atazanavir if they are not concurrently taking tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). However, in order to achieve target drug concentrations, adolescents may require doses of atazanavir that are higher than those recommended for use in adults (see Pediatric Use).
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend use of unboosted atazanavir.

Adolescent and Adult Dose
- Treatment-Naive Patients:
  - Atazanavir/ritonavir (ATV/r) 300 mg/100 mg once daily with food.
  - Atazanavir/cobicistat (ATV/c) is currently not approved by the FDA for use in children or adolescents aged <18 years.
  - Atazanavir 400 mg once daily with food. If unboosted atazanavir is used in adolescents, higher doses than those used in adults may be required to achieve target drug concentrations (see Pediatric Use).
  - Emtricitabine/TAF is approved for use with ATV/r in patients weighing ≥35 kg.
- Treatment-Experienced Patients:
  - ATV/r 300 mg/100 mg once daily with food.
  - ATV/c 300 mg/150 mg once daily with food, or coformulated Evotaz once daily with food.
  - ATV/c is currently not approved by the FDA.
pump inhibitors. ART-naive patients who are receiving proton-pump inhibitors should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before taking boosted atazanavir. Coadministration of atazanavir with proton-pump inhibitors is not recommended in ART-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients who had marked elevations in transaminases before treatment may have an increased risk of further elevations in transaminases or hepatic decompensation.
- Atazanavir oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet of oral powder contains 35 mg of phenylalanine.

Powder Administration:
- Mix atazanavir oral powder with at least 1 tablespoon of soft food (e.g., applesauce, yogurt). Oral powder mixed with a beverage (at least 30 mL of milk or water) may be used for older infants who can drink from a cup.
  - For young infants (aged <6 months) who cannot eat solid food or drink from a cup, oral powder should be mixed with at least 10 mL of infant formula and given using an oral dosing syringe.
- Administer ritonavir immediately following powder administration.
- Administer the entire dose of oral powder within 1 hour of preparation.

Metabolism/Elimination
- Atazanavir is a substrate and inhibitor of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronyl transferase 1A1.

Atazanavir Dosing in Patients with Hepatic Impairment:
- Atazanavir should be used with caution in patients with mild or moderate hepatic impairment. Consult the manufacturer’s prescribing information for the dose adjustment in patients with moderate impairment.
- Atazanavir should not be used in patients with severe hepatic impairment.
Atazanavir Dosing in Patients with Renal Impairment:
- No dose adjustment is required for patients with renal impairment.
- Atazanavir should not be given to ART-experienced patients with end-stage renal disease who are on hemodialysis.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- **Metabolism:** Atazanavir is both a substrate and an inhibitor of the cytochrome P450 (CYP) 3A4 enzyme system and has significant interactions with drugs that are highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. Atazanavir is a weak inhibitor of CYP2C8. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucuronoyl transferase (UGT1A1). Because there is potential for multiple drug interactions with atazanavir, a patient’s medication profile should be carefully reviewed for potential drug interactions before atazanavir is administered.

- **Nucleoside reverse transcriptase inhibitors (NRTIs):** Tenofovir disoproxil fumarate (TDF) decreases atazanavir plasma concentrations. Only atazanavir/ritonavir (ATV/r) should be used in combination with TDF. The effect of tenofovir alafenamide (TAF) on unboosted atazanavir is unknown; thus, only ATV/r should be used with TAF.

- **Non-nucleoside reverse transcriptase inhibitors:** Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be coadministered to patients who are receiving atazanavir (with or without ritonavir). Efavirenz should not be coadministered with atazanavir in antiretroviral therapy (ART)-experienced patients, but this drug may be used in combination with ritonavir-boosted atazanavir 400 mg in ART-naive adults. Although ATV/r should be taken with food, efavirenz should be taken on an empty stomach, preferably at bedtime.

- **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. The dosage for atazanavir should be adjusted when it is administered with medications that alter gastric pH. Guidelines for the appropriate doses of atazanavir to use with antacids, H2 receptor antagonists, and proton-pump inhibitors in adults are complex and can be found on the package insert for atazanavir. No information is available on the...
appropriate doses of atazanavir to use in children when the drug is coadministered with medications that alter gastric pH.

- Coadministering cobicistat, a CYP3A4 inhibitor, and medications that are metabolized by CYP3A4 may increase the plasma concentrations of these medications. This may increase the risk of clinically significant adverse reactions (including life-threatening or fatal reactions) that are associated with the concomitant medications. Coadministration of cobicistat, atazanavir, and CYP3A4 inducers may lead to lower exposures of cobicistat and atazanavir, a loss of efficacy of atazanavir, and possible development of resistance.\(^1\) Coadministering cobicistat and atazanavir with some antiretroviral (ARV) agents (e.g., with etravirine, with efavirenz in ART-experienced patients, or with another ARV that requires pharmacokinetic [PK] enhancement, such as another protease inhibitor [PI] or elvitegravir) may result in decreased plasma concentrations of that agent, leading to loss of therapeutic effect and the development of resistance.

**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 paresthesia.

- **Less common:** Prolongation of the PR interval. Abnormalities in atroventricular (AV) conduction are generally limited to first-degree AV block, but there have been reports of second-degree AV block. Rash, generally mild or moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other PIs. 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. Chronic kidney disease, including biopsy-proven cases of granulomatous interstitial nephritis that were associated with the deposition of atazanavir drug crystals in the renal parenchyma have occurred. Nephrolithiasis and cholelithiasis have been reported. Hepatotoxicity (patients with hepatitis B virus or hepatitis C virus infections are at increased risk of hepatotoxicity).

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

**Pediatric Use**

**Approval**

Atazanavir is approved by the Food and Drug Administration (FDA) for use in infants (aged ≥3 months and weighing ≥5 kg), children, and adolescents.

**Efficacy**

Studies in treatment-naive adults have shown that ATV/r is as effective as efavirenz and lopinavir/ritonavir (LPV/r) when these drugs are administered with two NRTIs.\(^2-5\) In ACTG A5257, ATV/r was compared to darunavir/ritonavir (DRV/r) or raltegravir, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, ATV/r was discontinued more frequently than the other regimens due to toxicity, most often hyperbilirubinemia or gastrointestinal complaints.\(^6\)

P1020 enrolled 195 ART-naive and ART-experienced patients with HIV aged 3 months to 21 years. Capsule and powder formulations and boosted and unboosted regimens were investigated in this open-label study; area under the curve (AUC) targeting was used to direct dose finding. Of the 195 patients enrolled, 142 patients received atazanavir-based treatment at the final recommended dose. Among them, 58% were ART-naive. At Week 48, 69.5% of the ART-naive patients and 43.3% of the ART-experienced patients had HIV viral loads ≤400 copies/mL.\(^7-8\)
Two open-label clinical trials in infants and children, PRINCE I and PRINCE II, studied a powder formulation of atazanavir that was administered once daily and boosted with liquid ritonavir.9-11 One hundred and thirty-four infants and children aged ≥3 months and weighing between 5 kg and 35 kg were evaluated. Using a modified intent-to-treat analysis, 28 of 52 ARV-naive patients (54%) and 41 of 82 ARV-experienced patients (50%) had HIV RNA <50 copies/mL at Week 48. The median increase from baseline in absolute CD4 T lymphocyte count at 48 weeks of therapy was 215 cells/mm³ (a 6% increase) in ARV-naive patients and 133 cells/mm³ (a 4% increase) in ARV-experienced patients.

**Pharmacokinetics and Dosing**

**Oral Capsule**

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 PK targets—but only when used at higher doses (on a mg/kg body weight or mg/m² body surface area basis) than the doses that are currently recommended in adults. In IMPAACT/PACTG 1020A, children aged >6 years to <13 years required 520 mg/m² per day of the atazanavir capsule formulation to achieve PK targets.8 Unboosted atazanavir at this dose was well tolerated in those aged <13 years who were able to swallow capsules.12 The approved dose of atazanavir for adults is 400 mg once daily without ritonavir boosting; however, adolescents aged >13 years required a dose of atazanavir 620 mg/m² per day.8 In this study, the AUCs for the unboosted arms were similar to those seen in the ATV/r arms, but the maximum plasma concentration (C_{max}) was higher and the minimum plasma concentration (C_{min}) was lower in the unboosted arms. Median doses of atazanavir, both with and without ritonavir boosting, from IMPAACT/PACTG 1020A are outlined in the table below. When administering unboosted atazanavir to pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.13 Higher target trough concentrations may be required in PI-experienced patients. IMPAACT P1058, a study of unboosted atazanavir PKs in ART-experienced children, concluded that once-daily atazanavir 400 mg provided suboptimal exposure and that administering higher unboosted doses or splitting the daily dose into twice-daily doses warranted investigation in ART-experienced children, adolescents, and young adults.14

Table A. Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A

<table>
<thead>
<tr>
<th>Age Range</th>
<th>ATV Given with RTV</th>
<th>ATV Median Dose (mg/m²)a</th>
<th>ATV Median Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–13 years</td>
<td>No</td>
<td>509</td>
<td>475</td>
</tr>
<tr>
<td>6–13 years</td>
<td>Yes</td>
<td>206</td>
<td>200</td>
</tr>
<tr>
<td>&gt;13 years</td>
<td>No</td>
<td>620</td>
<td>900</td>
</tr>
<tr>
<td>&gt;13 years</td>
<td>Yes</td>
<td>195</td>
<td>350</td>
</tr>
</tbody>
</table>

*a These doses 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.


**Key to Acronyms:** AUC = area under the curve; ATV = atazanavir; PK = pharmacokinetic; RTV = ritonavir; TDM = therapeutic drug monitoring

In the report of the IMPAACT/ PACTG P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m² in pediatric subjects when administered with ritonavir.15 A study of a model-based approach that used atazanavir concentration-time data from three adult studies and one pediatric study (P1020A),16 along with subsequent additional adjusted modeling,17 informed the use of the following weight-based ATV/r doses that are listed in the current, FDA-approved product label for children aged ≥6 years to <18 years:

- Weighing 15 kg to <35 kg: ATV/r 200 mg/100 mg
- Weighing ≥35 kg: ATV/r 300 mg/100 mg

**Cobicistat as a Pharmacokinetic Enhancer**

A study of 14 adolescents, aged 12 years to 18 years, suggests that cobicistat is a safe and effective PK enhancer.
enhancer when used in combination with atazanavir in adolescent patients.\textsuperscript{18}

**Oral Powder**

The unboosted atazanavir powder arms in IMPAACT/PACTG P1020A were closed because participants were unable to achieve target exposures. For the IMPAACT/PACTG P1020A trial, AUC targets (30,000 to 90,000 ng*hr/mL) were established based on exposures in adults in early studies of unboosted atazanavir. In IMPAACT/PACTG P1020A, children aged 3 months to 2 years who were in the boosted atazanavir powder cohorts and who received a daily dose of atazanavir 310 mg/m\textsuperscript{2} achieved average atazanavir exposures that approached, but did not meet, protocol targets. Variability in exposures was high, especially among the very young children in this age range.\textsuperscript{8}

Assessment of the PKs, safety, tolerability, and virologic response of atazanavir oral powder for FDA approval was based on data from two open-label, multicenter clinical trials:

- PRINCE I, which enrolled pediatric patients aged 3 months to <6 years;\textsuperscript{9} and
- PRINCE II, which enrolled pediatric patients aged 3 months to <11 years.\textsuperscript{10}

One hundred and thirty-four treated patients (weighing 5 kg to <35 kg) from both studies were evaluated during the FDA approval process. All patients in the PRINCE trials were treated with boosted atazanavir and two NRTIs. Children received an oral solution that contained atazanavir and ritonavir. Doses were assigned according to the child’s weight:

- Weighing 5 kg to <10 kg: Atazanavir 150 mg or atazanavir 200 mg and ritonavir 80 mg
- Weighing 10 kg to <15 kg: Atazanavir 200 mg and ritonavir 80 mg
- Weighing 15 kg to <25 kg: Atazanavir 250 mg and ritonavir 80 mg
- Weighing 25 kg to <35 kg: Atazanavir 300 mg and ritonavir 100 mg

No new safety concerns were identified during these trials. The FDA label includes the following PK parameters that were measured during the PRINCE trials, including mean AUC, for the weight ranges that correspond to the recommended doses:

**Table B. Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE I and II)\textsuperscript{a} versus Capsules in Young Adults\textsuperscript{a} and Adults\textsuperscript{b}**

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>PRINCE Trial\textsuperscript{b} ATV/r</th>
<th>PRINCE Trial\textsuperscript{b} ATV/r</th>
<th>PRINCE Trial\textsuperscript{b} ATV/r</th>
<th>PRINCE Trial\textsuperscript{b} ATV/r</th>
<th>PRINCE Trial\textsuperscript{b} ATV/r</th>
<th>Young Adult Study\textsuperscript{a}</th>
<th>Adult Study\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC ng•h/mL</td>
<td>Dose: 150 mg/80 mg Weighing: 5 kg to &lt;10 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td>Dose: 200 mg/80 mg Weighing: 5 kg to &lt;10 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td>Dose: 250 mg/80 mg Weighing: 10 kg to &lt;15 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td>Dose: 300 mg/100 mg Weighing: ≥25 kg to &lt;35 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C\textsubscript{24h} ng/mL</td>
<td>Dose: 150 mg/80 mg Weighing: 5 kg to &lt;10 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td>Dose: 200 mg/80 mg Weighing: 5 kg to &lt;10 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td>Dose: 250 mg/80 mg Weighing: 10 kg to &lt;15 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td>Dose: 300 mg/100 mg Weighing: ≥25 kg to &lt;35 kg Mean\textsuperscript{c} (CV% or 95% CI) [N]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>336 (76%) [20]</td>
<td>550 (60%) [10]</td>
<td>572 (111%) [18]</td>
<td>678 (69%) [31]</td>
<td>578 (474–704) [22]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} The young adults were also receiving TDF.\textsuperscript{7}

\textsuperscript{b} This information comes from the Reyataz package insert.\textsuperscript{10}

\textsuperscript{c} Means are geometric means.

**Key to Acronyms:** ATV/r = atazanavir/ritonavir; AUC = area under the curve; CI = confidence interval; CV = coefficient of variation; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

While the PK targets were met in these PK studies of atazanavir powder in all patients except those who received ATV/r 150 mg/80 mg in the 5 kg to <10 kg weight band, there were large coefficients of variation.
especially among the youngest patients.

**Transitioning from Powder to Capsules**

For children who reach a weight ≥25 kg while taking the powder, atazanavir 300 mg powder (six packets) plus ritonavir 100 mg oral solution, both administered once daily with food, may be used. Atazanavir capsules should be used for children who can swallow pills. Bioavailability is higher for the capsules than for the powder; therefore, a lower mg/kg dose is recommended when using capsules. Opened capsules have not been studied and should not be used.

**Toxicity**

Nine percent of patients enrolled in the IMPAACT/PACTG 1020A trial had a bilirubin ≥5.1 times the upper limit of normal.\(^9\)\(^1\) Nine percent of patients enrolled in the PRINCE studies had a total bilirubin ≥2.6 times the upper limit of normal.\(^9\)\(^1\) The most common laboratory abnormality during the PRINCE trials was elevated amylase levels, which occurred in 33% of patients.\(^10\) Three children (2%) had treatment-related cardiac disorders during the PRINCE trials: one child discontinued therapy due to QTC prolongation and two experienced first-degree AV block.\(^9\)\(^1\) In IMPAACT/PACTG P1020A, three children (3%) had QTC prolongations >470 msec; two of these children came off study, and all were asymptomatic.

**References**


