Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Atazanavir (ATV, Reyataz)  
(Last updated May 22, 2018; last reviewed May 22, 2018)

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  
Fixed-Dose Combination Tablets  
•  [Evotaz] Atazanavir 300 mg plus cobicistat 150 mg

Generic Formulations  
Capsules: 150 mg, 200 mg, 300 mg  
Capsules and powder packets are not interchangeable.

Dosing Recommendations

Neonate Dose:  
•  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).

Pediatric Dose

Powder Formulation:  
•  Powder formulation must be administered with ritonavir.  
•  Not approved for use in infants aged <3 months or weighing <5 kg.

Infants and Children (Aged ≥3 Months; Weighing ≤5 kg)  
Atazanavir Powder:

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Once-Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg to &lt;15 kg</td>
<td>Atazanavir 200 mg (4 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food</td>
</tr>
<tr>
<td>15 kg to &lt;25 kg</td>
<td>Atazanavir 250 mg (5 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food</td>
</tr>
</tbody>
</table>

Capsule Formulation:

•  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 atroventricular block in some patients  
•  Nephrolithiasis  
•  Increased serum transaminases  
•  Hyperlipidemia (primarily with ritonavir boosting)

Special Instructions

•  Administer atazanavir with food to enhance absorption.  
•  Capsules and powder packets are not interchangeable.  
•  Do not open capsules.

Powder Administration:

•  Mix atazanavir oral powder with at least 1 tablespoon of 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.
•  Because atazanavir can prolong the

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### Children (Aged ≥6 Years; Weighing ≥15 kg):

**Atazanavir Capsules**

<table>
<thead>
<tr>
<th>Weight (kg)</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 200 mg plus ritonavir 100 mg, both once daily with food</td>
</tr>
<tr>
<td>≥35 kg</td>
<td>Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food</td>
</tr>
</tbody>
</table>

For Treatment-Naive Pediatric Patients Who Do Not Tolerate Ritonavir:

- Atazanavir powder must be administered with ritonavir.
- For capsule formulation, atazanavir/ritonavir (ATV/r) is preferred for children and adolescents. Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted atazanavir in children aged <13 years. 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](#)).
- Only ATV/r should be used in combination with tenofovir disoproxil fumarate (TDF), because TDF decreases atazanavir exposure.

### Adolescent and Adult Dose

**Treatment-Naive Patients**

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.
- Atazanavir 300 mg plus cobicistat 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Atazanavir/cobicistat is currently not FDA-approved for use in children 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](#)).

**Treatment-Experienced Patients**

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.
- Atazanavir 300 mg plus cobicistat 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Atazanavir/cobicistat is currently not FDA-approved for use in children aged <18 years.

### Metabolism/Elimination

- Atazanavir is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).

**Atazanavir Dosing in Patients with Hepatic Impairment**

- Atazanavir should be used with caution in patients with mild or moderate hepatic impairment; consult manufacturer’s prescribing information for dose adjustment in patients with moderate impairment.
- Atazanavir should not be used in patients with

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Atazanavir in Combination with Efavirenz (Adults) in
Treatment-Naive Patients Only:
• Atazanavir 400 mg plus ritonavir 100 mg plus
  efavirenz 600 mg, all once daily at separate
times.
• Although ATV/r should be taken with food,
  efavirenz should be taken on an empty
  stomach, preferably at bedtime. Efavirenz
  should not be co-administered with atazanavir
  (with or without ritonavir) in treatment-
  experienced patients, because efavirenz
decreases atazanavir exposure.

Atazanavir in Combination with TDF (Adults):
• Atazanavir 300 mg plus ritonavir 100 mg plus
  TDF 300 mg, all once daily with food.
• Atazanavir 300 mg plus cobicistat 150 mg
  plus TDF 300 mg, all once daily with food.
  Atazanavir/cobicistat is currently not FDA-
  approved for use in children aged <18 years.
• Only boosted atazanavir should be used in
  combination with TDF, because TDF decreases
  atazanavir exposure.

Atazanavir Dosing in Patients with Renal
Impairment:
• No dose adjustment is required for patients
  with renal impairment.
• Atazanavir should not be given to treatment-
  experienced patients with end-stage renal
disease who are on hemodialysis.

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

• 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. Atazanavir is a weak inhibitor of CYP2C8.
  Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucuronosyltransferase (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.

• 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.

*a mg/kg dosing is higher for the powder packets than for the capsules. Bioavailability was higher for the capsules than for the powder
when studied in adults.

*b For a child weighing ≥25 kg who cannot swallow atazanavir capsules, atazanavir 300 mg (6 packets) oral powder plus ritonavir 100
mg oral solution, both once daily with food, may be used.

*c Either ritonavir capsules or ritonavir oral solution can be used.

*d For adult patients who cannot swallow capsules, atazanavir oral powder is taken once daily with food at the same adult dose as the
capsules, along with ritonavir.

*e See the cobicistat section for important information about toxicity, drug interactions, and monitoring of patients who receive
  cobicistat and the combination of cobicistat and TDF.
• **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. Atazanavir dosage should be adjusted when it is administered with medications that alter gastric pH. Guidelines for dosing atazanavir 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 dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.

• **Co-administering cobicistat, a CYP3A4 inhibitor, and medications metabolized by CYP3A4 may increase plasma concentrations of these medications. This may increase the risk of clinically significant adverse reactions (including life-threatening or fatal reactions) associated with the concomitant medications. Co-administration of cobicistat with atazanavir in combination with CYP3A4 inducers may lead to lower exposure of cobicistat and atazanavir, loss of efficacy of atazanavir, and possible development of resistance.**

Co-administration of cobicistat and atazanavir with some antiretroviral (ARV) agents (e.g., with etravirine, with efavirenz in treatment-experienced patients, 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 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 PR interval of electrocardiogram (ECG). Abnormalities in atrioventricular (AV) conduction are generally limited to first-degree AV block, but with rare 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 associated with the deposition of atazanavir drug crystals in the renal parenchyma,** nephrolithiasis. Hepatotoxicity (patients with hepatitis B virus or hepatitis C virus infections are at increased risk).

**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 Food and Drug Administration (FDA)-approved for use in infants (aged >3 months and weighing ≥5 kg), children, and adolescents.

**Efficacy**

ATV/r has efficacy equivalent to efavirenz-based and lopinavir/ritonavir (LPV/r)-based combination therapy when given in combination with two NRTIs in treatment-naive adults. 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.

P1020 enrolled 195 antiretroviral therapy (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, PRINCE I and PRINCE II, studied a powder formulation of atazanavir administered once daily and boosted with liquid ritonavir in infants and children aged ≥3 months and weighing ≥5 kg.\(^9,10\) One hundred and thirty-four infants and children weighing between 5 kg and 35 kg were evaluated. Using a modified intent-to-treat analysis, overall proportions of ARV-naive and ARV-experienced patients with HIV RNA <50 copies/mL at Week 48 were 54% (28/52) and 50% (41/82), respectively. The median increase from baseline in absolute CD4 T lymphocyte count (percent) at 48 weeks of therapy was 215 cells/mm\(^3\) (6%) in ARV-naive patients and 133 cells/mm\(^3\) (4%) 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 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 aged >6 to <13 years required atazanavir dosing of 520 mg/m\(^2\) per day of 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.\(^11\) Doses required for older adolescents were greater than the approved dose for adults of atazanavir 400 mg given without ritonavir boosting once daily; adolescents aged >13 years required atazanavir dosing of 620 mg/m\(^2\) per day.\(^8\) In this study, the AUCs for the unboosted arms were similar to the ATV/r groups but the maximum plasma concentration (C\(_{\text{max}}\)) was higher and the minimum plasma concentration (C\(_{\text{min}}\)) was 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 is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.\(^12\) Higher target trough concentrations may be required in PI-experienced patients. IMPAACT P1058, a study of unboosted atazanavir PKs in treatment-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 treatment-experienced children, adolescents, and young adults.\(^13\)

**Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A\(^8\)**

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>ATV Given with RTV</th>
<th>ATV Median Dose (mg/m(^2))(^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>208</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>

\(^a\) 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.

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

In the report of the P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m\(^2\) in pediatric subjects when dosed with ritonavir.\(^14\) A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A),\(^15\) along with subsequent additional adjusted modeling,\(^16\) 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 to <18 years:
• 200/100 mg (15 kg to <35 kg)
• 300/100 mg (≥35 kg)

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 when used in combination with atazanavir in adolescent patients.13

Oral Powder

The unboosted atazanavir powder cohorts in IMPAACT/PACTG P1020A were closed based on the inability to achieve target exposures. For the IMPAACT/PACTG P1020A trial, AUC targets were established based on exposures in adults in early studies of unboosted atazanavir. For that study, target AUC range was 30,000 to 90,000 ng*hr/mL. Boosted atazanavir powder cohorts in IMPAACT/PACTG P1020A in children aged 3 months to 2 years, using a dose of 310 mg/m² daily, achieved average atazanavir exposures that approached but did not meet protocol targets. Variability in exposures was greater, especially among the very young children in this age range.8

Assessment of the PK, safety, tolerability, and virologic response of atazanavir oral powder for FDA approval was based on data from 2 open-label, multicenter clinical trials:

• PRINCE I: In pediatric patients aged 3 months to <6 years9
• PRINCE II: In pediatric patients aged 3 months to <11 years10

One hundred and thirty-four treated patients (weighing 5 kg to <35 kg) from both studies were evaluated. All patients in the PRINCE trials were treated with boosted atazanavir and two NRTIs. Patients weighing 5 kg to <10 kg received either 150 mg or 200 mg atazanavir and 80 mg ritonavir oral solution, 10 kg to <15 kg received 200 mg atazanavir and 80 mg ritonavir oral solution, 15 kg to <25 kg received 250 mg atazanavir and 80 mg ritonavir oral solution, and 25 kg to <35 kg received 300 mg atazanavir and 100 mg ritonavir oral solution. No new safety concerns were identified in these trials. The FDA label includes the following PK parameters measured in the PRINCE trials, including mean AUC, for the weight ranges that correspond to the recommended doses:

Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE I and II)a versus Capsules in Young Adultsb and Adultsa

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>PRINCE Triala ATV/r Dose 150/80 (mg) Body Weight (kg) 5 to &lt;10</th>
<th>PRINCE Triala ATV/r Dose 200/80 (mg) Body Weight (kg) 5 to &lt;10</th>
<th>PRINCE Triala ATV/r Dose 200/80 (mg) Body Weight (kg) 10 to &lt;15</th>
<th>PRINCE Triala ATV/r Dose 250/80 (mg) Body Weight (kg) 15 to &lt;25</th>
<th>PRINCE Triala ATV/r Dose 300/100 (mg) Body Weight (kg) ≥25 to &lt;35</th>
<th>Young Adult Studya</th>
<th>Adult Studya</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC ng*h/mL Mean (CV% or 95% CI) [n]</td>
<td>32,503 (61%) [20]</td>
<td>39,519 (54%) [10]</td>
<td>50,305 (67%) [18]</td>
<td>55,525 (46%) [31]</td>
<td>44,329 (63%) [8]</td>
<td>35,971 (30,853–41,898) [22]</td>
<td>46,073 (66%) [10]</td>
</tr>
<tr>
<td>C24 ng/mL Mean (CV% or 95% CI) [n]</td>
<td>336 (76%) [20]</td>
<td>550 (60%) [10]</td>
<td>572 (111%) [18]</td>
<td>678 (69%) [31]</td>
<td>468 (104%) [8]</td>
<td>578 (474–704) [22]</td>
<td>636 (97%) [10]</td>
</tr>
</tbody>
</table>

a Reyataz package insert.10
b The young adults were also receiving TDF.7
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 but the ATV/r 150/80 mg dose in the 5 kg to <10 kg weight band, there were large coefficients of variation (CV)%, especially in the youngest patients.

Transitioning from Powder to Capsules

For children who reach a weight ≥25 kg while taking the powder, atazanavir 300 mg (6 packets) powder plus ritonavir oral solution 100 mg, both once daily with food, may be used. Atazanavir capsules should be used for children who can swallow pills. Bioavailability was higher for the capsules than for the powder when studied in adults; therefore, a lower mg/kg dose is recommended. 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. Asymptomatic ECG abnormalities were observed in a small number of patients: Grade 3 QTC prolongation in one patient, Grade 2 PR or HR changes in nine patients, and Grade 3 PR prolongations in three patients. No significant changes in serum cholesterol or triglycerides were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with two NRTIs.

References


