



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Atazanavir (ATV, Reyataz) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Capsules and powder packets are not interchangeable.

Dosing Recommendations

Neonate Dose:

- Not approved for use in neonates and infants younger than 3 months. Atazanavir should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric Dose

Powder Formulation:^a

- Powder formulation must be administered with ritonavir.
- Not approved for use in infants aged <3 months or weighing less than 5 kg.

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

Atazanavir Powder^a

Weight (kg)	Once-Daily Dose
5 to <15 kg	Atazanavir 200 mg (4 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food
15 to <25 kg ^b	Atazanavir 250 mg (5 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food

Capsule Formulation:^a

- Not approved for use in children <6 years or <15 kg

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular 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 such as applesauce or 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 (<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 dosage of oral powder within 1 hour of preparation.
 - Because atazanavir can prolong the ECG

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

Atazanavir Capsules^a

Weight (kg)	Once-Daily Dose
<15 kg	Capsules not recommended
15 to <20 kg	Atazanavir 150 mg plus ritonavir ^c 100 mg, both once daily with food
20 to <40 kg ^d	Atazanavir 200 mg plus ritonavir ^c 100 mg, both once daily with food
≥40 kg	Atazanavir 300 mg plus ritonavir ^c 100 mg, both once daily with food

For Treatment-Naïve 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-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

Antiretroviral-Naïve Patients:

- Atazanavir 300 mg plus ritonavir 100 mg once daily with food.^e
- Atazanavir 300 mg plus cobicistat^f 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 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](#)]).

Antiretroviral-Experienced Patients:

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.^e
- Atazanavir 300 mg plus cobicistat^f 150 mg,

PR interval, use atazanavir 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).

- Atazanavir absorption is dependent on low gastric pH; therefore, when atazanavir is administered with medications that alter gastric pH, special dosing information is indicated (see Drug Interactions using the [atazanavir package insert](#)). When administered with buffered didanosine formulations or antacids, give atazanavir at least 2 hours before or 1 hour after antacid or didanosine administration.
- The plasma concentration, and therefore therapeutic effect, of atazanavir can be expected to decrease substantially when atazanavir is co-administered with proton-pump inhibitors. Antiretroviral therapy-naïve patients receiving proton-pump inhibitors (PPIs) should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted atazanavir. Co-administration of atazanavir 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.
- Atazanavir oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet contains 35 mg of phenylalanine.

Metabolism/Elimination

- Atazanavir is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).
- Dosing of atazanavir in patients with hepatic impairment: Atazanavir 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. Atazanavir should not be used in patients with severe hepatic impairment.
- Dosing of atazanavir in patients with renal

both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.

impairment: No dose adjustment is required for patients with renal impairment. However, atazanavir should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

Atazanavir in Combination with Efavirenz (Adults) in Treatment-Naïve Patients Only:

- Atazanavir 400 mg plus ritonavir 100 mg plus efavirenz 600 mg, all once daily at separate times.^e
- 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.^e
- Atazanavir 300 mg plus cobicistat^f 150 mg plus TDF 300 mg, all once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.
- Only boosted atazanavir should be used in combination with TDF because TDF decreases atazanavir exposure.

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

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

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

^d Some experts would increase atazanavir to 300 mg at ≥ 35 kg to avoid under-dosing, especially when administered with TDF (see text for discussion).

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

^f See Cobicistat section for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat and the combination of cobicistat and TDF.

Drug Interactions (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- **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. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucuronosyltransferase (UGT1A1). A patient's medication profile should be carefully reviewed for potential drug interactions with atazanavir before the drug 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-naïve 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. Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton-pump inhibitors in adults are complex and can be found in the prescribing information brochure. No information is available on dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.
- Initiation of cobicistat, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving cobicistat may increase plasma concentration of these medications, which 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 CYP3A inducers may lead to lower exposure of cobicistat and atazanavir and loss of efficacy of atazanavir and possible 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 (EKG). Abnormalities in atrioventricular (AV) conduction generally limited to first-degree AV block, but with rare reports of second-degree 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 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 preexisting 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://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

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 in Clinical Trials:

- 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-naïve adults.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 antiretroviral therapy (ART)-naïve and ART-experienced patients with HIV infection aged 3 months to 21 years. Capsule and powder formulations and boosted and unboosted regimens were studied in this open-label study; targeted area under the curve (AUC)-directed dose finding. Of the 195 patients enrolled, 142 patients received atazanavir-based treatment at the final recommended dose. Among them, 58% were ART-naïve. At week 48, 69.5% of the naïve patients and 43.3% of the experienced patients had HIV viral loads ≤ 400 copies/mL.^{7,8}
- Atazanavir in a powder formulation administered once daily boosted with liquid ritonavir was studied in infants and children aged ≥ 3 months and weighing ≥ 5 kg in 2 open-label clinical trials, PRINCE I and PRINCE II.^{9,10} One hundred and thirty-four infants and children weighing between 5 and 35 kg were evaluated. Using a modified intent-to-treat analysis, overall proportions of antiretroviral (ARV)-naïve and ARV-experienced patients with HIV RNA < 50 copies/mL at Week 48 were 54% (28/452) and 50% (41/82), respectively. The median increase from baseline in absolute CD4 T lymphocyte (CD4) count (percent) at 48 weeks of therapy was 215 cells/mm³ (6%) in ARV-naïve patients and 133 cells/mm³ (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/m² 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/m² 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 adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily; adolescents aged >13 years required atazanavir dosing of 620 mg/m² 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_{\max}) was higher and minimum plasma concentration (C_{\min}) lower for the unboosted arms. Median doses of atazanavir in mg/m² 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.

Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A⁸

Age Range (Years)	ATV Given with RTV	ATV Median Dose (mg/m ²) ^a	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

^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: AUC = area under the curve; ATV = atazanavir; PK = pharmacokinetic; RTV = ritonavir

In the report of the P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m² in pediatric subjects when dosed with ritonavir.¹ However, given the available atazanavir capsule dose strengths, it is not possible to administer the exact mg dose equivalent to the body surface area-based dose. 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 weight-based ATV/r doses that are listed in the current FDA-approved product label for children aged ≥ 6 to < 18 years:

- 150/100 mg (15 to < 20 kg)
- 200/100 mg (20 to < 40 kg)
- 300/100 mg (≥ 40 kg)¹³

The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling.¹³ The authors acknowledge that ATV/r at 250/100 mg appeared to be a more appropriate dose than ATV/r at 200/100 mg for the 35 to < 40 kg weight group; however, this dose is not achievable with current capsule dose strengths (150, 200, and 300 mg).¹³ Some experts would increase atazanavir to 300 mg at ≥ 35 kg to avoid underdosing, especially when administered with TDF.

Cobicistat as a Pharmacokinetic Enhancer

No data are available on the use of cobicistat in pediatric patients.

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

134 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 2 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 Adults^b and Adults^a

PK Parameters	Prince Trial ^a ATV/r Dose 150/80 (mg) Body Weight (kg) 5 to <10	Prince Trial ^a ATV/r Dose 200/80 (mg) Body Weight (kg) 5 to <10	Prince Trial ^a ATV/r Dose 200/80 (mg) Body Weight (kg) 10 to <15	Prince Trial ^a ATV/r Dose 250/80 (mg) Body Weight (kg) 15 to <25	Prince Trial ^a ATV/r Dose 300/100 (mg) Body Weight (kg) ≥25 to <35	Young Adult Study ^b	Adult Study ^a
AUC ng•h/mL Mean ^c (CV% or (95% CI) [n])	32,503 (61%) [20]	39,519 (54%) [10]	50,305 (67%) [18]	55,525 (46%) [31]	44,329 (63%) [8]	35,971 (30,853–41,898) [22]	46,073 (66%) [10]
C24 ng/mL Mean ^c (CV% or (95% CI) [n])	336 (76%) [20]	550 (60%) [10]	572 (111%) [18]	678 (69%) [31]	468 (104%) [8]	578 (474–704) [22]	636 (97%) [10]

^a Reyataz package insert¹⁰

^b The young adults were also receiving TDF.⁸

^c Means are geometric means.

Key to Acronyms: ATV/r = atazanavir/ritonavir; AUC = area under the curve; CI = confidence interval; CV = coefficient of variation

While the PK targets were met in these PK studies of atazanavir powder in all but the ATV/r 150/80 mg dose, 5 to <10 kg weight band, there were large coefficient 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, 300 mg (6 packets) atazanavir 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 is 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.¹¹ Asymptomatic EKG 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 were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs.¹⁰

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