

Atazanavir (Reyataz, ATV)

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Summary

- Atazanavir (ATV) concentrations are reduced during pregnancy.
 - Only ritonavir-boosted ATV (ATV/r) should be used in pregnancy, as drug levels are too low if unboosted ATV or cobicistat (COBI)-boosted ATV (ATV/c) is used in pregnancy.
 - ATV levels are further reduced when given concomitantly with tenofovir disoproxil fumarate (TDF) or an H2-receptor antagonist.
 - Increased dose (ATV/r 400 mg/100 mg once daily with food) during the second and third trimesters is used routinely by some experts; this increased dose should be used if ATV is given concomitantly with TDF or an H2-receptor antagonist.
- First-trimester exposure to ATV is not associated with increased risk of congenital anomalies.
- Protease inhibitor (PI)-based regimens, including ATV/r, may be associated with increased rates of preterm delivery.

Human Studies in Pregnancy

Pharmacokinetics

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of using ATV/r during pregnancy.¹ Overall, most pregnant women achieved undetectable HIV RNA at the time of delivery in these studies.²⁻⁷

In studies that evaluated full PK profiles of daily ATV/r 300 mg/100 mg during pregnancy, the ATV area under the curve (AUC) was lower during pregnancy than the ATV AUC reported in other studies of nonpregnant adults with HIV.^{2,5,6,8} In one of the studies, no difference was observed in the ATV AUC during pregnancy and postpartum, but the AUC at both times was lower than the AUC observed in historic, nonpregnant controls with HIV.⁵ In the other studies, the ATV AUC was lower during pregnancy than it was in the same patients postpartum and in nonpregnant control populations.^{2,4,6,8} Intracellular ATV levels in women taking ATV/r 300 mg/100 mg appear stable throughout pregnancy.⁹ Genetic variants appear to partially explain the interpatient variability in third-trimester ATV exposure seen in pregnant women who receive ATV/r.¹⁰

ATV/r combined with TDF and emtricitabine (FTC) provides a complete, once-daily antiretroviral therapy regimen for use during pregnancy. However, the ATV AUC of pregnant women in the third trimester who received concomitant TDF was 30% lower than the ATV AUC of women who were not receiving concomitant TDF, an effect similar to that seen in nonpregnant adults.^{6,8} The magnitude of the increase in ATV AUC postpartum relative to ATV AUC in the third trimester in women taking concomitant TDF was similar to that in women not taking concomitant TDF.⁶ On the other hand, a smaller PK study demonstrated that concomitant TDF did not result in a lower ATV AUC or a higher risk of ATV trough concentrations (C_{trough}) <0.15 mg/L (the target C_{trough} for antiretroviral-naïve patients) in pregnant women during their third trimester.¹¹ In a therapeutic drug monitoring (TDM)

study of 103 women (most of whom were African) in Paris, the proportions of women with an ATV C_{trough} of <0.15 mg/L were similar for women who did and women who did not take concomitant TDF.⁷

In studies that evaluated the use of once-daily ATV/r 400 mg/100 mg during pregnancy,^{2,4} pregnant women who received this increased dose without TDF had an ATV AUC that was equivalent to the ATV AUC seen in historic, nonpregnant controls with HIV who received the standard ATV 300-mg dose without TDF. Pregnant women who received the increased ATV 400-mg dose with TDF had an ATV AUC equivalent to that seen in nonpregnant patients with HIV who received the standard ATV 300-mg dose with TDF.^{2,4} Although some experts recommend an increased dose of ATV for all patients during the second and third trimesters of pregnancy, the package insert recommends the use of an increased dose of ATV during the second and third trimesters only for antiretroviral-experienced pregnant women who also are receiving either TDF or an H2-receptor antagonist. TDM of ATV in pregnancy may also be useful.¹² For additional details about interactions between concomitant medications, please see [Drug-Drug Interactions](#) in the [Adult and Adolescent Antiretroviral Guidelines](#).

The pharmaco-enhancing effect of COBI on ATV is impacted during pregnancy. Pregnant women who received ATV boosted with COBI had trough ATV concentrations (C_{trough}) that were 66% and 72% lower during the second and third trimesters, respectively, **compared with paired postpartum data ($P = 0.0625$ and $P = 0.0313$, respectively).**¹³ Concomitant use of ATV and COBI is **not recommended** during pregnancy because of these substantial reductions in drug exposures (see [Cobicistat](#)).¹⁴

Placental and Breast Milk Passage

In studies of women receiving ATV/r combination therapy during pregnancy, cord blood ATV concentration averaged 13% to 21% of maternal serum levels at delivery.^{3,5,6}

In a study of three women, the median ratio of breast milk ATV concentration to plasma ATV concentration¹⁵ was 0.13.

Teratogenicity/Adverse Pregnancy Outcomes

In a multicenter study that evaluated a U.S. cohort of children who were exposed to HIV but who did not contract HIV, first-trimester ATV exposure was associated with increased odds of congenital anomalies of the skin (adjusted odds ratio [aOR] 5.24; $P = 0.02$) and the musculoskeletal system (aOR 2.55; $P = 0.007$).¹⁶ On the other hand, there was no association between first-trimester ATV exposure and birth defects in a French cohort, although this study¹⁷ had $<50\%$ power to detect an aOR of 1.5. The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to ATV in humans to be able to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of cardiovascular and genitourinary defects (the most common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with ATV. Among the cases of first-trimester ATV exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was **2.5%** (**36** of **1,464** live births; 95% confidence interval [CI], **1.7%** to **3.4%**) compared with a **2.8%** total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.¹⁸

Please see [Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes](#) for a discussion of the potential association between the use of boosted PIs and preterm delivery.

Other Safety Data

Elevation in indirect (unconjugated) bilirubin that can be attributed to ATV-related inhibition of the hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with ATV, including during pregnancy.¹⁹ It is unknown whether elevated maternal indirect bilirubin throughout pregnancy has any effects on the fetus. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received ATV during pregnancy.^{2,3,5,6,20-22} In some studies, neonatal bilirubin elevations that require treatment with phototherapy occur more frequently after prenatal ATV exposure. However, decisions to use phototherapy frequently are subjective, and guidelines for phototherapy vary across countries, making it difficult to compare the severity of hyperbilirubinemia among patients within a study and across different studies.^{20,21} Elevated neonatal bilirubin in neonates exposed to ATV is not associated with UGT-1 genotypes that have been linked to decreased UGT function.²²

In an evaluation of neurodevelopmental outcomes in 374 infants aged 9 to 15 months who were exposed to HIV but who did not contract HIV, the adjusted mean scores on the language and social-emotional domains of the Bayley-III test were significantly lower for infants with perinatal exposure to ATV than for infants who were exposed to other drugs.^{23,24} In a study of language assessments among 792 children aged 1 to 2 years who were exposed to HIV but who did not contract HIV, children with ATV exposure had an increased risk of late language emergence at age 12 months (aOR 1.83; 95% CI, 1.10–3.04) compared to children without ATV exposure, but this association was not significant at 24 months.²⁵

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis was reported in 3 of 38 ATV-exposed infants who had glucose samples collected during the first day of life. All three hypoglycemic infants' glucose samples were adequately collected and processed in a timely fashion.³ This report of infant hypoglycemia is similar to a prior report in which two of 14 infants who were exposed to PIs (i.e., nelfinavir, saquinavir, or indinavir) developed hypoglycemia during the first day of life; both infants with hypoglycemia had been exposed to nelfinavir.²⁶

Animal Studies

Carcinogenicity

In *in vitro* and *in vivo* assays, ATV shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with ATV. In female mice, the incidence of benign hepatocellular adenomas increased at systemic exposures that were 2.8-fold to 2.9-fold higher than those seen in humans who received the recommended therapeutic dose (ATV 300 mg boosted with ritonavir [RTV] 100 mg once daily). There was no increase in the incidence of tumors in male mice at any dose and no significant increase in the incidence of neoplasms in rats at systemic exposures up to 1.1-fold (in males) or 3.9-fold (in females) higher than those seen in humans who received the recommended therapeutic dose.³

Reproduction/Fertility

No effect of ATV on reproduction or fertility in male and female rodents was observed at drug exposure levels (as measured by AUC) that were 0.9-fold (in males) and 2.3-fold (in females) higher than the exposures achieved in humans who received the recommended therapeutic dose.³

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, no evidence of teratogenicity was observed in offspring born to animals that had systemic ATV exposure levels (as measured by AUC) that were 0.7 times (in rabbits) and 1.2 times (in rats) those observed in humans who received the recommended therapeutic dose. In developmental toxicity studies in rats, maternal dosing (through pregnancy and lactation) that produced systemic ATV exposure that was 1.3 times the human exposure resulted in reversible neonatal growth retardation. However, offspring were unaffected at lower maternal doses that produced systemic drug exposures equivalent to those observed in humans who received the recommended therapeutic dose.³ A separate study demonstrated an association between maternal PI use (including the use of ATV) and lower progesterone levels, which correlated with lower birthweight in mice.^{27,28} Maternal administration of ATV (with TDF/FTC or abacavir/lamivudine) was associated with delayed postnatal (infant) growth and neurodevelopment in mice.²⁹

Placental and Breast Milk Passage

ATV maternal-to-fetal (transplacental) transfer is reduced, possibly because ATV is a substrate of the p-glycoprotein, which is an adenosine triphosphate-binding cassette transporter responsible for drug efflux across the placenta.³⁰

ATV is excreted in the milk of lactating rats. Maternal ATV use in rats that produced systemic ATV exposure that was 1.3 times the human exposure was associated with neonatal growth restriction that reversed after weaning.³

Excerpt from [Table 14](#)

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in [Appendix B](#) and [Table 14](#) in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations ^a	Use in Pregnancy
<p>Atazanavir (ATV) <i>Reyataz</i></p> <p>Note: Generic products are available for some formulations.</p> <p>Note: ATV must be combined with low-dose RTV boosting in pregnancy.</p> <p>(ATV/c) <i>Evotaz</i></p>	<p>ATV (Reyataz)</p> <p><i>Capsules</i></p> <ul style="list-style-type: none"> • 100 mg (generic product only) • 150 mg^c (generic product only) • 200 mg^c • 300 mg^c <p><i>Oral Powder</i></p> <ul style="list-style-type: none"> • 50-mg packet <p>ATV/c (Evotaz)</p> <ul style="list-style-type: none"> • ATV 300-mg/COBI 150-mg tablet 	<p>Pregnancy</p> <p><i>PKs in Pregnancy</i></p> <ul style="list-style-type: none"> • ATV (Reyataz) <ul style="list-style-type: none"> ○ ATV concentrations are reduced during pregnancy, and they are further reduced when ATV is given concomitantly with TDF or an H2-receptor antagonist. • ATV/c (Evotaz) <ul style="list-style-type: none"> ○ Use of ATV/c is not recommended during pregnancy, because ATV trough concentrations are 80% to 85% lower than the ATV concentrations seen in nonpregnant adults. <p><i>Dosing in Pregnancy</i></p> <ul style="list-style-type: none"> • ATV (Reyataz) <ul style="list-style-type: none"> ○ Use of unboosted ATV is not recommended during pregnancy. ○ Use of ATV is not recommended during pregnancy for ARV-experienced patients who are taking TDF and an H2-receptor antagonist. ○ Use of an increased dose (ATV/r 400 mg/100 mg once daily with food) during the second and third trimesters results in plasma ATV concentrations equivalent to those seen in nonpregnant adults receiving standard dosing. Although some experts recommend increased ATV dosing in all patients during the second and third trimesters of pregnancy, the package insert recommends increased ATV 	<p>Low placental transfer to fetus^b</p> <p>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)</p> <p>Must be given with RTV boosting in pregnancy</p> <p>Effect of <i>in utero</i> ATV exposure on infant indirect bilirubin levels is unclear. Nonpathologic elevations of neonatal bilirubin have been observed in some, but not all, clinical trials to date.</p> <p>Oral powder (but not capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria.</p> <p>Use of ATV/c is not recommended during pregnancy. See Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 6 and Table 7 for discussions about avoiding the use of ATV/c during pregnancy.</p>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations ^a	Use in Pregnancy
		<p>dosing only for ARV-experienced pregnant people in the second and third trimesters who are also receiving either TDF or an H2-receptor antagonist.</p> <ul style="list-style-type: none"> • ATV/c (Evotaz) <ul style="list-style-type: none"> ○ ATV/c should not be used in pregnancy because atazanavir C_{min} is substantially reduced (see COBI). <p>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI).</p> <p>Standard Adult Doses</p> <p><i>In ARV-Naive Patients Without RTV Boosting</i></p> <ul style="list-style-type: none"> • ATV 400 mg once daily with food; ATV without RTV boosting is not recommended when used with TDF, H2-receptor antagonists, PPIs, or during pregnancy. <p><i>In ARV-Naive Patients With RTV Boosting</i></p> <ul style="list-style-type: none"> • ATV/r 300 mg/100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV/r 400 mg/100 mg once daily with food <p><i>In ARV-Experienced Patients</i></p> <ul style="list-style-type: none"> • ATV 300 mg plus RTV 100 mg once daily with food • Do not use with PPIs or EFV. <p><i>In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist</i></p> <ul style="list-style-type: none"> • ATV/r 300/100 mg once daily with food 	

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations ^a	Use in Pregnancy
		<p><i>In ARV-Experienced Patients Who Are Receiving an H2-Receptor Antagonist and TDF</i></p> <ul style="list-style-type: none"> • ATV/r 400 mg/100 mg once daily with food <p><i>Powder Formulation</i></p> <ul style="list-style-type: none"> • Oral powder is taken with RTV once daily with food at the same recommended adult dose as the capsules. <p><i>ATV/c (Evotaz)</i></p> <ul style="list-style-type: none"> • One tablet once daily with food 	

^a Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 11](#)).

^b Placental transfer categories are determined by mean or median cord blood-to-maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

^c Generic product is available.

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; COBI = cobicistat; EFV = efavirenz; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

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