



**Recommendations for the Use of Antiretroviral Drugs in
Pregnant Women with HIV Infection and Interventions to Reduce
Perinatal HIV Transmission in the United States**

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Protease Inhibitors

Glossary of Terms for Supplement

Carcinogenic: Producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

Clastogenic: Causing disruption of or breakages in chromosomes

Genotoxic: Damaging to genetic material such as DNA and chromosomes

Mutagenic: Inducing or capable of inducing genetic mutation

Teratogenic: Interfering with fetal development and resulting in birth defects

For information regarding the protease inhibitor (PI) class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see [Combination Antiretroviral Drug Regimens and Pregnancy Outcome](#).

Atazanavir (Reyataz, ATV)

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According to the Food and Drug Administration, available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate.¹

Animal Studies

Carcinogenicity

In *in vitro* and *in vivo* assays, atazanavir shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. In female mice, the incidence of benign hepatocellular adenomas increased at systemic exposures that were 2.8- to 2.9-fold higher than those seen in humans who received the recommended therapeutic dose (atazanavir 300 mg boosted with ritonavir 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 rates 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.¹

Reproduction/Fertility

No effect of atazanavir on reproduction or fertility in male and female rodents was seen at area under the curve (AUC) levels 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.¹

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals that had systemic atazanavir exposure levels (AUC) 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 that produced systemic atazanavir exposure 1.3 times the human exposure resulted in maternal toxicity in weight loss or suppression of weight gain in the offspring. 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.¹ A more recent study demonstrated an association between maternal protease inhibitor (PI) use (including atazanavir) and lower progesterone levels, which correlated with lower birthweight in mice.^{2,3}

Placental and Breast Milk Passage

Atazanavir is excreted in the milk of lactating rats. Maternal atazanavir use in rats was associated with neonatal growth restriction that reversed after weaning.¹

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Human Studies in Pregnancy

Pharmacokinetics

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of using atazanavir/ritonavir (ATV/r) during pregnancy.⁴ Overall, most pregnant women achieved undetectable HIV RNA at the time of delivery.^{1,5-9} In a retrospective study that measured trough atazanavir concentrations at a median of 30 weeks' gestation in 19 pregnant women (including 14 who were in the third trimester of pregnancy) who received atazanavir 300 mg and ritonavir 100 mg once daily, all but two women had a trough atazanavir concentration >100 ng/mL.¹⁰ In studies that evaluated full PK profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy, atazanavir AUC was lower during pregnancy than the AUC reported in other studies of nonpregnant adults with HIV infection.^{5,7,8,11,12} In one of the studies, there was no difference between atazanavir AUC during pregnancy and postpartum, but AUC at both times was lower than that of nonpregnant historic controls with HIV infection.⁷ In the other studies, atazanavir AUC was lower during pregnancy than it was in the same patients postpartum and in nonpregnant control populations.^{5,6,8,11,12} **Intracellular atazanavir levels in women taking atazanavir 300 mg given with ritonavir 100 mg appear to be stable throughout pregnancy.**¹³

ATV/r combined with tenofovir disoproxil fumarate (TDF) and emtricitabine provides a complete, once-a-day antiretroviral therapy (ART) regimen for pregnant women. However, the atazanavir AUC of pregnant women in the third trimester who received concomitant TDF was 30% lower than the atazanavir AUC of women who were not receiving concomitant TDF, an effect similar to that seen in nonpregnant adults.^{8,11} The increase in atazanavir AUC postpartum relative to that in the third trimester was similar for women taking concomitant TDF and for those not taking concomitant TDF.⁸ On the other hand, a smaller PK study demonstrated that concomitant TDF did not result in lower atazanavir AUC or higher risk of trough concentration <0.15 mg/L (the target for treatment-naïve patients) in pregnant women in their third trimester.¹⁴ In a therapeutic drug monitoring (TDM) study of 103 women (mostly African) in Paris, there was no difference in the risk of atazanavir trough concentration <0.15 mg/L between women who did and women who did not take concomitant TDF.⁹

In studies that investigated a dose of atazanavir 400 mg with ritonavir 100 mg once daily during pregnancy,^{5,6} pregnant women receiving the increased dose without TDF had an atazanavir AUC equivalent to that seen in historic nonpregnant controls with HIV infection who received standard-dose atazanavir without TDF. Pregnant women who received the increased atazanavir dose with TDF had an atazanavir AUC equivalent to that seen in nonpregnant patients with HIV infection who received standard-dose atazanavir with TDF.^{5,6} Although some experts recommend an increased dose of atazanavir for all women during the second and third trimesters, the package insert recommends the use of an increased dose of atazanavir in the second and third trimesters only for antiretroviral (ARV)-experienced pregnant women who are also receiving either TDF or an H2-receptor antagonist. TDM of atazanavir in pregnancy may also be useful.¹⁵ For additional details about interactions between concomitant medications, please see [Drug-Drug Interactions](#) in the [Adult and Adolescent Guidelines](#).

The combination of atazanavir and cobicistat has not been directly studied in pregnant women; however, limited data from studies of cobicistat as a pharmacoenhancer for other ARV drugs in pregnant women suggest that cobicistat exposure is substantially reduced in pregnancy^{16,17} (see [Cobicistat](#) section). Thus, there are insufficient data to make a recommendation about the use of atazanavir/cobicistat in pregnant women.

Placental and Breast Milk Passage

In studies of women receiving ATV/r combination therapy during pregnancy, cord blood atazanavir concentration averaged 13% to 21% of maternal serum levels at delivery.^{1,7,8}

In a study of three women, the median ratio of breast milk atazanavir concentration to plasma atazanavir concentration was 13%.¹⁸

Teratogenicity/Adverse Pregnancy Outcomes

In a multicenter, U.S. cohort of children who were exposed to HIV but who did not contract HIV, first-trimester atazanavir 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; $P = 0.007$).¹⁹ On the other hand, there was no association between first-trimester atazanavir exposure and birth defects in a French cohort, although this study had <50% power to detect an aOR of 1.5.²⁰ The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to atazanavir in humans to be able to detect at least a 1.5-fold increase in risk of overall birth defects, and no such increase in birth defects has been observed with atazanavir. The prevalence of birth defects with first-trimester atazanavir exposure was 2.2% (28 of 1,279 births; 95% CI, 1.5% to 3.2%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.²¹

Please see [Combination 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 atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir, including during pregnancy.²² 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 atazanavir during pregnancy.^{1,5,7,8,10,23-25} In some studies, neonatal bilirubin elevations that require treatment with phototherapy occur more frequently after prenatal atazanavir 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 between patients within a study and across different studies.^{23,24} Elevated neonatal bilirubin in neonates exposed to atazanavir is not associated with UGT-1 genotypes that are associated with decreased UGT function.²⁵

In an evaluation of neurodevelopmental outcomes in 374 infants ages 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 atazanavir than for infants exposed to other drugs.^{26,27} In a study of language assessments among 792 children (ages 1 to 2 years) who were exposed to HIV but who did not contract HIV, children with atazanavir 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 atazanavir exposure, but the association was not significant at 24 months.²⁸

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis has been reported in three of 38 atazanavir-exposed infants with glucose samples collected during the first day of life. All three hypoglycemic infants' glucose samples were adequately collected and processed in a timely fashion.¹ This finding of infant hypoglycemia is similar to a prior report in which two of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia during the first day of life; both infants with hypoglycemia had been exposed to nelfinavir.²⁹

Excerpt from Table 10^a

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<p>Atazanavir (ATV) <i>Reyataz</i></p> <p>Note: Generic available for some formulations.</p> <p>Note: ATV must be combined with low-dose RTV boosting in pregnancy.</p> <p>(ATV/COBI) <i>Evotaz</i></p>	<p><u>ATV (Reyataz)</u></p> <p><u>Capsules:</u></p> <ul style="list-style-type: none"> • 100 mg (generic product only) • 150 mg^d • 200 mg^d • 300 mg^d <p><u>Oral Powder:</u></p> <ul style="list-style-type: none"> • 50 mg packet <p><u>ATV/COBI (Evotaz):</u></p> <ul style="list-style-type: none"> • ATV 300 mg plus COBI 150 mg tablet 	<p><u>Standard Adult Doses</u></p> <p><u>ARV-Naive Patients</u></p> <p><u>Without RTV Boosting:</u></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><u>With RTV Boosting:</u></p> <ul style="list-style-type: none"> • ATV 300 mg plus RTV 100 mg once daily with food • When combined with EFV in ARV-naive patients: ATV 400 mg plus RTV 100 mg once daily with food <p><u>ARV-Experienced Patients:</u></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><u>If Combined with an H2-Receptor Antagonist:</u></p> <p>ATV 300 mg plus RTV 100 mg once daily with food</p> <p><u>If Combined with an H2-Receptor Antagonist and TDF:</u></p> <ul style="list-style-type: none"> • ATV 400 mg plus RTV 100 mg once daily with food <p><u>Powder Formulation:</u></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><u>ATV/COBI (Evotaz):</u></p> <ul style="list-style-type: none"> • 1 tablet once daily with food <p><u>PK in Pregnancy</u></p> <p><u>ATV (Reyataz):</u></p> <ul style="list-style-type: none"> • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H2-receptor antagonist. <p><u>ATV/COBI (Evotaz):</u></p> <ul style="list-style-type: none"> • No PK studies in human pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI). <p><u>Dosing in Pregnancy</u></p> <p><u>ATV (Reyataz):</u></p> <ul style="list-style-type: none"> • Use of unboosted ATV is not recommended during pregnancy. • Use of ATV is not recommended for ARV-experienced pregnant women taking TDF and an H2-receptor antagonist. • Use of an increased dose (ATV 400 mg plus RTV 100 mg once daily with food) during the second and third trimesters results in plasma ATV concentrations equivalent to those seen in nonpregnant adults on standard dosing. Although some experts recommend increased ATV dosing in all women during the second and third trimesters, the package insert recommends increased ATV dosing only for ARV-experienced pregnant women in the second and third trimesters who are also receiving either TDF or an H2-receptor antagonist. <p><u>ATV/COBI (Evotaz):</u></p> <ul style="list-style-type: none"> • Insufficient data to make dosing recommendation in pregnancy (see Cobicistat section). 	<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 as low-dose RTV-boosted regimen in pregnancy.</p> <p>Effect of <i>in utero</i> ATV exposure on infant indirect bilirubin levels is unclear. Nonpathologic elevations of neonatal hyperbilirubinemia 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>ATV/COBI is not recommended for use in pregnancy. For women who become pregnant while taking ATV/COBI, consider switching to a more effective, recommended regimen. If an ATV/COBI regimen is continued, doses should be administered with food; viral load should be monitored frequently.</p>

Excerpt from Table 10^a

^a Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Guidelines, Appendix B, Table 8](#)).

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

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

^d Generic formulation available

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; EFV = efavirenz; **FDC = fixed-dose combination**; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

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