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

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Carcinogenic</td>
<td>Producing or tending to produce cancer</td>
</tr>
<tr>
<td></td>
<td>• Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.</td>
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<tr>
<td></td>
<td>• Genetic mutations and/or chromosomal damage can contribute to cancer formation.</td>
</tr>
<tr>
<td>Clastogenic</td>
<td>Causing disruption of or breakages in chromosomes</td>
</tr>
<tr>
<td>Genotoxic</td>
<td>Damaging to genetic material such as DNA and chromosomes</td>
</tr>
<tr>
<td>Mutagenic</td>
<td>Inducing or capable of inducing genetic mutation</td>
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<tr>
<td>Teratogenic</td>
<td>Interfering with fetal development and resulting in birth defects</td>
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</table>

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)**

*(Last updated November 14, 2017; last reviewed November 14, 2017)*

According to the Food and Drug Administration, atazanavir has been evaluated in a limited number of women during pregnancy, and 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 was increased at systemic exposures 2.8- to 2.9-fold higher than those in humans at the recommended therapeutic dose (300 mg atazanavir boosted with 100 mg ritonavir once daily). There was no increase in the incidence of tumors in male mice at any dose. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 1.1-fold (males) or 3.9-fold (females) higher than those in humans at 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 compared with the exposures achieved in humans at the recommended therapeutic dose.¹

*Teratogenicity/Adverse Pregnancy Outcomes*

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg atazanavir boosted with 100 mg ritonavir once daily). In developmental toxicity studies in rats, maternal dosing that produced systemic drug exposure 1.3 times the human exposure resulted in maternal toxicity, and also resulted in weight loss or suppression of weight gain in the offspring. However, offspring were unaffected at lower maternal doses that produced systemic drug exposure equivalent to that observed in humans at the recommended therapeutic dose.¹ A more recent study demonstrated an association of maternal PI use (including atazanavir) with 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 and was associated with neonatal growth restriction that reversed after weaning.1

Human Studies in Pregnancy

Pharmacokinetics

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of atazanavir/ritonavir in pregnancy.4 Overall, most pregnant women achieved undetectable HIV RNA at the time of delivery.1,5,9 In a retrospective study reporting trough atazanavir concentrations at a median of 30 weeks’ gestation (14 in the third trimester) in 19 pregnant women receiving atazanavir 300 mg and ritonavir 100 mg once daily, all but 2 women had a trough atazanavir concentration >100 ng/mL.10 In studies that have 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 in historic data from non-pregnant 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 in non-pregnant 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 non-pregnant control populations.5,6,8,11,12

Atazanavir/ritonavir 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 in pregnant women in the third trimester receiving concomitant TDF compared with women who were not receiving concomitant TDF was 30% lower, an effect similar to that seen in non-pregnant 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 did not demonstrate that concomitant TDF resulted in lower atazanavir AUC or higher risk of trough <0.15 mg/L (target for treatment-naive patients) in pregnant women in their third trimester.13 In a therapeutic drug monitoring (TDM) study of 103 women (mostly African) in Paris, there was no difference in risk of atazanavir trough <0.15 mg/L between women who did and those who did not take concomitant TDF.9

In studies investigating an increased dose of atazanavir of 400 mg with 100 mg ritonavir once daily during pregnancy,5,6 pregnant women receiving the increased dose without TDF had an atazanavir AUC equivalent to that seen in historic non-pregnant controls with HIV infection receiving standard-dose atazanavir without TDF. Pregnant women receiving the increased atazanavir dose with TDF had an AUC equivalent to that seen in non-pregnant patients with HIV infection receiving standard-dose atazanavir with TDF.5,6 Although some experts recommend increased atazanavir dosing in all women during the second and third trimesters, the package insert recommends increased atazanavir dosing in the second and third trimesters only for antiretroviral-experienced pregnant women who are also receiving either TDF or an H2-receptor antagonist. TDM of atazanavir in pregnancy may also be useful.14 For additional details about dosing with interacting concomitant medications, please see Drug Interactions in the Adult and Adolescent Guidelines.

Placental and Breast Milk Passage

In studies of women receiving atazanavir/ritonavir 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 3 women, the median ratio of breast milk atazanavir concentration to that in plasma was 13%.15

Teratogenicity/Adverse Pregnancy Outcomes

In a multicenter, U.S. cohort of children exposed to HIV who were uninfected, first-trimester atazanavir exposure was associated with increased odds of congenital anomalies of skin (aOR = 5.24, P = 0.02) and musculoskeletal system (aOR = 2.55, P = 0.007).16 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 adjusted odds ratio of 1.5.17 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 2.1% (26 of 1,227 births; 95% CI, 1.4% to 3.1%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.18

Maternal PI use (including atazanavir) was associated with lower progesterone levels, but the clinical significance of this finding requires further study.2 In a different study, PI-based ART regimens were associated with elevated levels of estradiol in maternal and cord blood of pregnant women living with HIV and these levels correlated with lower birth weight percentile.19

Other Safety Data
Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir, including during pregnancy.20 The effects on the fetus of elevated maternal indirect bilirubin throughout pregnancy are unknown. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received atazanavir during pregnancy.1,5,7,8,10,21-23 Although some studies have suggested that neonatal bilirubin elevations requiring phototherapy occur more frequently after prenatal atazanavir exposure, decisions to use phototherapy to treat infants with hyperbilirubinemia frequently are subjective and guidelines for phototherapy of infants vary between countries, making it difficult to compare the severity of hyperbilirubinemia between patients within a study and in different studies.21,22 Elevated neonatal bilirubin in neonates exposed to atazanavir is not associated with UGT-1 genotypes associated with decreased UGT function.23

In an evaluation of neurodevelopmental outcomes in 374 infants aged 9 to 15 months who were exposed to HIV but were uninfected, the adjusted mean score on the language and social-emotional domains of the Bayley-III test was significantly lower for infants with perinatal exposure to atazanavir compared to those with exposure to other drugs.24,25 In a study of language assessments among 792 children (aged 1 and 2 years) who were exposed to HIV but were uninfected, children with atazanavir exposure had an increased risk of late language emergence at age 12 months (adjusted odds ratio 1.83, 95% CI, 1.10–3.04) compared with children without atazanavir exposure but the association was not significant at 24 months.26

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 in 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 2 (both nelfinavir) of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia in the first day of life.27
<table>
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<th>Generic Name (Abbreviation) Trade Name</th>
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</table>
| Atazanavir (ATV) Reyataz              | Capsules:  • 150 mg  • 200 mg  • 300 mg Oral Powder:  • 50 mg packet Evotaz:  • ATV 300 mg plus COBI 150 mg tablet | **Standard Adult Dose** Atazanavir (Reyataz) ARV-Naive Patients Without RTV Boosting: • ATV 400 mg once daily with food; ATV without RTV boosting is not recommended when used with TDF, H2-receptor antagonists, or PPIs, or during pregnancy. With RTV Boosting: • 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 | Low placental transfer to fetus. 
No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Must be given as low-dose RTV-boosted regimen in pregnancy. Effect of in utero ATV exposure on infant indirect bilirubin levels is unclear. Non-pathologic elevations of neonatal hyperbilirubinemia have been observed in some but not all clinical trials to date. Oral powder (but not capsules) contains phenylalanine, which can be harmful to patients with phenylketonuria. |
| Atazanavir/Cobicistat (ATV/COBI) Evotaz | 1 tablet once daily with food. | **PK in Pregnancy** Atazanavir (Reyataz): • ATV concentrations reduced during pregnancy; further reduced when given concomitantly with TDF or H2-receptor antagonist. Atazanavir/Cobicistat (Evotaz): • No PK studies in human pregnancy. | **Dosing in Pregnancy** Atazanavir (Reyataz): • Use of unboosted ATV is not recommended during pregnancy. • Use of ATV not recommended for treatment-experienced pregnant women taking TDF and an H2-receptor antagonist. • Use of an increased dose (400 mg ATV plus 100 mg RTV once daily with food) during the second and third trimesters results in plasma concentrations equivalent to those in non-pregnant 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 also receiving either TDF or an H2-receptor antagonist. Atazanavir/Cobicistat (Evotaz): • Insufficient data to make dosing recommendation in pregnancy (see Cobicistat section). |

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* Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 7).

* Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

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

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; EFV = efavirenz; PK = pharmacokinetic; PPI = proton pump inhibitors; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

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