



**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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Pharmaco-Enhancers

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

Cobicistat (Tybost, COBI)

(Last updated December 7, 2018, last reviewed December 7, 2018)

Cobicistat has insufficient data on human use in pregnancy to inform a drug-associated risk determination for birth defects or miscarriage.

Animal Studies

Carcinogenicity

At cobicistat exposures 7 times and 16 times the human systemic exposure, no increases in tumor incidence were seen in male and female mice. In rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses up to twice the typical human exposure. The follicular cell findings are considered rat-specific and not relevant to humans.¹

Reproduction/Fertility

No effect has been seen on fertility in male or female rats.¹

Teratogenicity/Adverse Pregnancy Outcomes

Studies in pregnant rats and rabbits have shown no evidence of teratogenicity, even with cobicistat exposures that were 1.4 times higher than the recommended human exposure in rats and 3.3 times higher than the recommended human exposure in rabbits.¹

Placental and Breast Milk Passage

No information is available on placental passage of cobicistat. Studies in rats have shown that cobicistat is secreted in breast milk.²

Human Studies in Pregnancy

Pharmacokinetics

Cobicistat pharmacokinetics (PKs) have been described in pregnant and postpartum women who were taking concomitant elvitegravir and darunavir. In a study of 30 pregnant women who were receiving elvitegravir/cobicistat, the area under the curve (AUC) for cobicistat was 44% lower in the second trimester and 59% lower in the third trimester than during the postpartum period. Trough cobicistat concentrations (24 hours post-dose) were 60% lower in the second trimester and 76% lower in the third trimester than during the postpartum period. Trough cobicistat concentrations were below the assay quantitation limit (<10 ng/mL) in 65% of women during the second trimester, 73% of women during the third trimester, and 24% of postpartum women.

The pharmaco-enhancing effect of cobicistat on elvitegravir was impacted during pregnancy; elvitegravir AUC was reduced by 44% and trough concentrations were reduced by 89% in the third trimester when compared to postpartum AUC and trough concentrations. Elvitegravir apparent oral clearance during

pregnancy and postpartum was negatively associated with cobicistat AUC.³ Study results reported in two conference abstracts have described decreases of similar magnitudes in cobicistat and darunavir exposures among pregnant women.^{4,5} In one of these abstracts, cobicistat AUC was decreased by 63% in the second trimester and 49% in the third trimester compared to AUC postpartum. Trough cobicistat concentrations decreased by 83% in both the second and third trimesters.

The pharmaco-enhancing effect of cobicistat on darunavir was also impacted during pregnancy; AUC based on total darunavir concentrations was 56% (in the second trimester) and 50% (in the third trimester) lower than AUC postpartum, and AUC based on unbound concentrations was 45% and 40% lower, respectively. The effect on darunavir trough concentrations was more pronounced, with both total and unbound concentrations showing essentially identical decreases of 92% (in the second trimester) and 88% to 89% (in the third trimester) compared to postpartum. One of six women in this study experienced virologic failure during the third trimester, and virologic failure continued through the postpartum period.⁴ Because of these substantial reductions in drug exposures during pregnancy, use of elvitegravir/cobicistat or darunavir/cobicistat **is not recommended** during pregnancy.^{6,7}

A study reported in a recent conference abstract evaluated tenofovir alafenamide (TAF) exposure when TAF was administered as a daily 10-mg dose with cobicistat 150 mg and found no differences between TAF exposure during pregnancy and TAF exposure in the same women postpartum. The authors concluded that no dose adjustment is needed during pregnancy for TAF when it is coadministered with cobicistat.⁸ However, TAF 10 mg with cobicistat is only available in fixed-dose combination products that also include either dolutegravir or elvitegravir, which are not recommended for use during pregnancy.

Placental and Breast Milk Passage

A study in 10 pregnant women receiving elvitegravir/cobicistat found a median cord blood to maternal delivery plasma cobicistat concentration ratio of 0.09. This study also found measurable concentrations of cobicistat in placental tissue and cord blood peripheral blood mononuclear cells (PBMC), with a cord/maternal PBMC ratio of 0.49.⁹ In another study, seven pregnant women who received elvitegravir/cobicistat had quantifiable cobicistat concentrations that were detectable in plasma at delivery. The median ratio for cord blood to maternal delivery plasma cobicistat concentration was 0.09. In 27 neonates born to mothers who were receiving elvitegravir/cobicistat, cobicistat was below the assay quantitation limit of 10 ng/mL in all washout PK samples taken between 2 hours and 9 days post-delivery.³ No data are available on breast milk passage of cobicistat in humans.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, five birth defects have been reported out of 204 live births to mothers with first-trimester exposure to cobicistat. The number of first-trimester exposures to cobicistat in humans is insufficient to be able to make a risk determination.²

Excerpt from Table 10^a (page 1 of 2)

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
Cobicistat (COBI) <i>Tyboost</i> (ATV/COBI) <i>Evotaz</i> (EVG/COBI/ FTC/TAF) <i>Genvoya</i> (DRV/COBI) <i>Prezcobix</i> (EVG/COBI/ FTC/TDF) <i>Stribild</i> (DRV/COBI/ FTC/TAF) Symtuza	<u>COBI (Tyboost)</u> <i>Tablet:</i> • COBI 150 mg <u>ATV/COBI (Evotaz):</u> • ATV/COBI 300 mg/50 mg tablet <u>EVG/COBI/FTC/TAF (Genvoya):</u> • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet <u>DRV/COBI (Prezcobix):</u> • DRV/COBI 800 mg/150 mg tablet <u>EVG/COBI/FTC/TDF (Stribild):</u> • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg tablet <u>DRV/COBI/FTC/TAF (Symtuza):</u> • DRV 800 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet	<u>Standard Adult Doses</u> <i>COBI (Tyboost):</i> • As an alternative PK booster with ATV or DRV: 1 tablet (150 mg) once daily with food <i>ATV/COBI (Evotaz):</i> • 1 tablet once daily with food <i>EVG/COBI/FTC/TAF (Genvoya):</i> • 1 tablet once daily with food <i>DRV/COBI (Prezcobix):</i> • 1 tablet once daily with food <i>EVG/COBI/FTC/TDF (Stribild):</i> • 1 tablet once daily with food <i>DRV/COBI/FTC/TAF (Symtuza):</i> • 1 tablet once daily with food <u>PK in Pregnancy:</u> • Based on limited data, COBI exposure and pharmacoenhancing effect on DRV and EVG are markedly reduced in pregnancy. • No data are available on the pharmacoenhancing effect of COBI on ATV. • When coadministered with COBI, TAF exposure is not significantly different between pregnancy and the postpartum period. <u>Dosing in Pregnancy:</u> • While COBI exposure is markedly reduced during pregnancy, higher than standard doses have not been studied. The Panel recommends RTV as the preferred pharmacoenhancer for PIs and INSTIs during pregnancy until more data are available on COBI activity during pregnancy. • For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF, TDF, ATV, DRV, EVG).	Low placental transfer to fetus. ^b Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. Use of COBI-boostered ATV, DRV, or EVG is not recommended in pregnancy.

^a Individual ARV drug doses 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

Key to Abbreviations: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; DRV = darunavir; EVG = elvitegravir; **FDC = fixed-dose combination**; FTC = emtricitabine; **INSTIs = integrase strand transfer inhibitors**; PIs = protease inhibitors; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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