

## Cobicistat (Tybost, COBI)

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### Summary

- Cobicistat (COBI) concentrations are decreased substantially—by approximately 45–85%—during pregnancy. The pharmaco-enhancing effects of COBI for atazanavir (ATV), darunavir (DRV), and elvitegravir (EVG) concentrations are similarly decreased.
- Although COBI exposure is reduced markedly during pregnancy, higher-than-standard doses have not been studied. The Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission does not recommend COBI for use with protease inhibitors and integrase strand transfer inhibitors during pregnancy; see [Table 7 Situation Specific Recommendations for Use of ARVs](#).
- First-trimester exposure to COBI is not associated with increased risk of congenital anomalies.

## Human Studies in Pregnancy

### Pharmacokinetics

COBI pharmacokinetics (PKs) have been described in pregnant and postpartum women who were taking concomitant EVG, ATV, and DRV. In a study of 30 pregnant women who were receiving elvitegravir/cobicistat (EVG/c), the area under the curve (AUC) for COBI was 44% lower in the second trimester and 59% lower in the third trimester than during the postpartum period. COBI trough concentrations ( $C_{\text{trough}}$ ) (24 hours postdose) were 60% lower in the second trimester and 76% lower in the third trimester than during the postpartum period. COBI  $C_{\text{trough}}$  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.<sup>1</sup> Another study of 14 women taking EVG/c reported COBI AUC reduced by 49% during pregnancy.<sup>2</sup> Two other studies have described decreases of similar magnitudes in COBI exposures when COBI is coadministered with DRV in pregnant women.<sup>3,4</sup> In one of these studies, COBI AUC was decreased by 63% in the second trimester and 49% in the third trimester compared to the AUC postpartum. COBI  $C_{\text{trough}}$  decreased by 83% in both the second and third trimesters.

The pharmaco-enhancing effect of COBI on EVG was impacted during pregnancy; EVG AUC was reduced by 44% and  $C_{\text{trough}}$  were reduced by 89% in the third trimester when compared to postpartum AUC and  $C_{\text{trough}}$ . EVG apparent oral clearance during pregnancy and postpartum was associated negatively with COBI AUC.<sup>5</sup> Similarly, another study reported that EVG  $C_{\text{trough}}$  were reduced by 77% in the third trimester, with 85% of women having EVG  $C_{\text{trough}}$  below the effective concentration ( $EC_{90}$ ).<sup>2</sup>

The pharmaco-enhancing effect of COBI on DRV and ATV also was reduced during pregnancy. Two studies have described DRV exposures with COBI boosting in pregnancy. In a study of 29 pregnant women, the AUC of DRV was reduced by 53% in the second trimester and 56% in the third trimester compared to postpartum.<sup>4</sup> In a smaller study of seven pregnant women, DRV AUC was reduced by 56% in the second trimester and 50% in the third trimester compared to postpartum. This study also reported unbound DRV concentrations, and unbound DRV AUC was 45% and 40% lower

during the second and third trimesters, respectively. The effect on DRV  $C_{\text{trough}}$  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) when compared to postpartum  $C_{\text{trough}}$ . One of six women in this study experienced virologic failure during the third trimester, and virologic failure continued through the postpartum period.<sup>3</sup> ATV  $C_{\text{trough}}$  were 80% and 85% lower in the second and third trimesters, respectively, compared to historical ATV  $C_{\text{trough}}$  in nonpregnant adults with HIV.<sup>1</sup> Because of these substantial reductions in drug exposures during pregnancy, use of COBI-boosted EVG, DRV, or ATV **is not recommended** for patients starting or changing regimens during pregnancy.<sup>6-8</sup>

One study evaluated tenofovir alafenamide (TAF) exposure in pregnant women when TAF was administered as a daily 10-mg dose with COBI 150 mg. No differences were seen between TAF exposure during pregnancy and TAF exposure postpartum in the same women. The authors concluded that no dose adjustment is needed during pregnancy for TAF when it is coadministered with COBI.<sup>9</sup> However, TAF 10 mg with COBI is available only in fixed-dose combination products that also include either DRV or EVG, which are not recommended for use during pregnancy. Another study described TAF exposure in pregnant women when administered as a 25-mg dose with a pharmaco-enhancer (either RTV 100 mg or COBI 150 mg). TAF exposures during pregnancy and postpartum did not differ.<sup>10</sup>

### **Placental and Breast Milk Passage**

A study in 10 pregnant women who received EVG/c found a median ratio of cord blood-to-maternal plasma COBI concentrations of 0.09. This study also found measurable concentrations of COBI in placental tissue and cord blood peripheral blood mononuclear cells (PBMC), with a cord blood-to-maternal PBMC ratio of 0.49.<sup>11</sup> In another study, median maternal plasma cobicistat concentration at delivery in 15 pregnant women was 172 ng/mL and cobicistat was quantifiable in cord blood from 7 of their deliveries with a median cord blood-to-maternal plasma ratio of 0.09.<sup>5</sup> In 27 neonates born to mothers who were receiving EVG/c, COBI was below the assay quantitation limit of 10 ng/mL in all washout PK samples taken between 2 hours and 9 days post-delivery.<sup>5</sup> No data are available on breast milk passage of COBI in humans.

### **Teratogenicity/Adverse Pregnancy Outcomes**

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to COBI to detect at least a twofold increase in the risk of overall birth defects in the general population. However, no such increase in the risk of birth defects has been observed with COBI. Among cases of first-trimester exposure to COBI that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.6% (18 of 509 live births; 95% confidence interval, 2.11% to 5.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>12</sup>

### ***Animal Studies***

#### **Carcinogenicity**

No increases in tumor incidence **relevant to humans** were seen in **rodent studies**.<sup>13</sup>

## **Reproduction/Fertility**

COBI did not affect fertility in male or female rats.<sup>6</sup>

## **Teratogenicity/Adverse Pregnancy Outcomes**

Studies in pregnant rats and rabbits have shown no evidence of teratogenicity, even with rat COBI exposures that were 1.4 times higher than the recommended human exposure and rabbit COBI exposures that were 3.3 times higher than the recommended human exposure.<sup>13</sup>

## **Placental and Breast Milk Passage**

No information is available on placental passage of COBI. Studies in rats have shown that COBI is secreted in breast milk.<sup>13</sup>

**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 <sup>a</sup>	Use in Pregnancy
<p><b>Cobicistat</b> (COBI) <i>Tybost</i></p> <p>(ATV/c) <i>Evotaz</i></p> <p>(EVG/c/FTC/TAF) <i>Genvoya</i></p> <p>(DRV/c) <i>Prezcobix</i></p> <p>(EVG/c/FTC/TDF) <i>Stribild</i></p> <p>(DRV/c/FTC/TAF) <i>Symtuza</i></p>	<p><b>COBI (Tybost)</b> <i>Tablet</i></p> <ul style="list-style-type: none"> <li>COBI 150 mg</li> </ul> <p><b>ATV/c (Evotaz)</b></p> <ul style="list-style-type: none"> <li>ATV 300-mg/COBI 50-mg tablet</li> </ul> <p><b>EVG/c/FTC/TAF (Genvoya)</b></p> <ul style="list-style-type: none"> <li>EVG 150-mg/COBI 150-mg/FTC 200-mg/TAF 10-mg tablet</li> </ul> <p><b>DRV/c (Prezcobix)</b></p> <ul style="list-style-type: none"> <li>DRV 800-mg/COBI 150-mg tablet</li> </ul> <p><b>EVG/c/FTC/TDF (Stribild)</b></p> <ul style="list-style-type: none"> <li>EVG 150-mg/COBI 150-mg/FTC 200-mg/TDF 300-mg tablet</li> </ul> <p><b>DRV/c/FTC/TAF (Symtuza)</b></p> <ul style="list-style-type: none"> <li>DRV 800-mg/COBI 150-mg/FTC 200-mg/TAF 10-mg tablet</li> </ul>	<p><b>Pregnancy</b></p> <p><i>PKs in Pregnancy</i></p> <ul style="list-style-type: none"> <li>Based on limited data, COBI exposure and its pharmacoenhancing effect on ATV, DRV, and EVG are reduced markedly in pregnancy.</li> <li>When coadministered with COBI, TAF exposure is not significantly different between pregnancy and the postpartum period.</li> </ul> <p><i>Dosing in Pregnancy</i></p> <ul style="list-style-type: none"> <li>Although COBI exposure is reduced markedly 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.</li> </ul> <p>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., <a href="#">FTC</a>, <a href="#">TAF</a>, <a href="#">TDF</a>, <a href="#">ATV</a>, <a href="#">DRV</a>, <a href="#">EVG</a>).</p> <p><b>Standard Adult Doses</b></p> <p><i>COBI (Tybost)</i></p> <ul style="list-style-type: none"> <li>When used as an alternative PK booster with ATV or DRV, the dose is one tablet once daily with food.</li> </ul>	<p>Low placental transfer to fetus<sup>b</sup></p> <p>No evidence of human teratogenicity (can rule out twofold increase in overall birth defects)</p> <p>Use of COBI-boosted ATV, DRV, or EVG is <b>not recommended</b> in pregnancy.</p>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations <sup>a</sup>	Use in Pregnancy
		<p><i>ATV/c (Evotaz)</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily with food</li> </ul> <p><i>EVG/c/FTC/TAF (Genvoya)</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily with food</li> </ul> <p><i>DRV/c (Prezcobix)</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily with food</li> </ul> <p><i>EVG/c/FTC/TDF (Stribild)</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily with food</li> </ul> <p><i>DRV/c/FTC/TAF (Symtuza)</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily with food</li> </ul>	

<sup>a</sup> 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](#)).

<sup>b</sup> 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:** ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; the Panel = The Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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