Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Cobicistat (Tybost, COBI)

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

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

Rats and rabbits treated with cobicistat during pregnancy at 1.4 and 3.3 times higher than the recommended human exposure have shown no evidence of teratogenicity.\(^1\)

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

A single case report found that cobicistat area under the curve (AUC) was reduced by 44% during the third trimester of pregnancy.\(^3\) A recent abstract described cobicistat pharmacokinetics (PK) in paired third-trimester and postpartum evaluations from 15 pregnant women taking concomitant elvitegravir. Cobicistat AUC was significantly reduced by 57% in the third trimester. Post-dose concentrations (at 24 hours) were reduced by at least 76%; cobicistat was below detection (<10 ng/mL) in most trough samples in pregnancy. Oral clearance of cobicistat was more than doubled during pregnancy.\(^4\) The pharmaco-enhancing effect of cobicistat on elvitegravir was impacted during pregnancy; elvitegravir AUC was reduced by 42% and trough concentrations were reduced by 87% in the third trimester compared to postpartum. No data are available on the impact of pregnancy on the pharmaco-enhancing activity of cobicistat for other coadministered antiretroviral drugs during pregnancy, such as darunavir or atazanavir.
Placental and Breast Milk Passage

No data are available on breast milk passage of cobicistat in humans. A study in 10 women found a median cord/maternal plasma 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. In 16 neonates, cobicistat was below detection in all washout PK samples taken between 2 hours and 9 days post-delivery.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, 1 birth defect has been reported in 83 live births with first-trimester exposure. The number of first-trimester exposures to cobicistat in humans is insufficient to be able to make a risk determination.

Excerpt from Table 9

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobicistat (COBI) Tybost</td>
<td>Tablet (Tybost): 150 mg</td>
<td>Standard Adult Dose Tybost: As an alternative PK booster with ATV or DRV/r: 1 tablet (150 mg) once daily with food.</td>
<td>Low placental transfer to fetus. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</td>
</tr>
<tr>
<td>Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine (EVG/COBI/TDF/FTC) Stribild</td>
<td>Tablet (Stribild): EVG 150 mg plus COBI 150 mg plus TDF 300 mg plus FTC 200 mg</td>
<td>Based on limited data, COBI exposure and pharmaco-enhancing effect are markedly reduced in pregnancy.</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (EVG/COBI/TAF/FTC) Genvoya</td>
<td>Tablet (Genvoya): EVG 150 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg</td>
<td>While COBI exposure is markedly reduced during pregnancy, higher than standard doses have not been studied. The Panel recommends the use of RTV as the preferred pharmaco-enhancer during pregnancy until more data are available on COBI activity during pregnancy.</td>
<td></td>
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<tr>
<td>Atazanavir/Cobicistat (ATV/COBI) Evotaz</td>
<td>Tablet (Evotaz): ATV 300 mg plus COBI 150 mg</td>
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<tr>
<td>Darunavir/Cobicistat (DRV/COBI) Prezcobix</td>
<td>Tablet (Prezcobix): DRV 800 mg plus COBI 150 mg</td>
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</tbody>
</table>

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

Key to Acronyms: ATV = atazanavir; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; EVG = elvitegravir; FTC = emtricitabine; PK = pharmacokinetic; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate

References