

Elvitegravir (EVG)

(Last updated December 29, 2020; last reviewed December 29, 2020)

Animal Studies

Carcinogenicity

In long-term studies of elvitegravir (EVG), no carcinogenicity was detected at exposures that were 14 fold higher (in mice and rats) and 27-fold higher (in rats) than those achieved in humans during systemic exposure to the recommended doses.¹

Reproduction/Fertility

EVG did not affect fertility in male and female rats at approximately 16-fold and 30-fold higher exposures than those seen in humans who received standard doses. Fertility was normal in the offspring of these rats.¹

Teratogenicity/Adverse Pregnancy Outcomes

Studies have shown no evidence of teratogenicity and no effect on reproductive function in rats and rabbits receiving EVG.¹

Placental and Breast Milk Passage

No data are available on the placental transfer of EVG in nonhuman primates. Studies in rats have demonstrated that EVG is secreted in breast milk.¹

Human Studies in Pregnancy

Pharmacokinetics

Pharmacokinetic (PK) and safety data from 30 pregnant U.S. women living with HIV who received a fixed-dose combination (FDC) of EVG, cobicistat (COBI), emtricitabine, and tenofovir disoproxil fumarate (TDF) have been published. EVG exposure (based on area under the curve [AUC]) was 24% lower during the second trimester and 44% lower during the third trimester than during the postpartum period. EVG trough concentration (C_{24h}) was 81% lower during the second trimester and 89% lower during the third trimester than during the postpartum period. COBI AUC was 54% to 57% lower and C_{24h} was 72% to 76% lower during the second and third trimesters, respectively, than during the postpartum period. EVG AUC failed to reach the exposure target of 23 mcg•h/mL (the 10th percentile for nonpregnant adults) in 50% of women during the second trimester and 55% of women during the third trimester; 12% of women reached the exposure target during the postpartum period. Plasma HIV RNA at delivery was <50 copies/mL in 19 of 25 women (76%) for whom data were available.² In a European study that evaluated the PK of EVG administered with COBI in 14 pregnant women, EVG AUC was reduced by 34% and trough concentration was reduced by 77% during the third trimester compared with the postpartum period. EVG trough concentration was below the EC_{90} (0.13 mg/L) in 85% of women in the third trimester and in none postpartum. Two women experienced virologic failure during the third trimester and were switched to alternative regimens.³

Two case reports of EVG and COBI PKs, safety, and efficacy in individual pregnant women found similar reductions in EVG and COBI exposure during pregnancy, although viral loads in both women remained undetectable throughout pregnancy.^{4,5} One case report described unbound EVG concentrations and found that the unbound fraction was 0.3% during pregnancy and 0.5% at 6 months postpartum. Reductions in both total EVG concentration and unbound EVG concentration increase the risk of suboptimal exposure.⁵

Because studies have reported reduced EVG exposure when pregnant women receive FDC tablets that contain EVG and COBI, the prescribing information for these products has been changed to indicate that these formulations are not recommended for use in pregnancy and should not be initiated in pregnancy; frequent viral load monitoring or use of an alternative regimen is recommended for individuals who become pregnant while

receiving these formulations.^{1,6} If these formulations are used in pregnancy, to maximize absorption, they should be administered with a meal and should not be administered within 2 hours of intake of preparations containing such minerals as iron or calcium, including prenatal vitamins.⁶

Placental and Breast Milk Passage

Placental passage of EVG has been evaluated in two studies. A U.S. study of EVG PK and safety observed that EVG crossed the placenta well, with a median cord-to-maternal-plasma ratio of 0.91 in 15 women. The median EVG elimination half-life in neonates was 7.6 hours, similar to that in nonpregnant adults. COBI concentrations were low in cord blood and were not detected in the plasma of any neonates.² A European study reported similar results, with a median cord blood-to-maternal delivery plasma ratio of 0.75 in seven women.³ No data are available on human breast milk transfer of EVG.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to EVG to allow the detection of at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with EVG.⁷ Among the cases of first-trimester EVG exposure, the prevalence of birth defects was 3.4% (11 of 323 live births; 95% confidence interval, 1.7% to 6.0%) compared with a 2.7% total prevalence in the U.S. population, according to Centers for Disease Control and Prevention surveillance.⁷ The Antiretroviral Pregnancy Registry reported supplemental data for central nervous system birth defect outcomes among 391 live births with exposure to EVG during periconception (n = 298) or pregnancy (late first trimester, n = 25; second or third trimester, n = 71). The Registry reported one central nervous system birth defect with exposure to EVG during periconception that was not a neural tube or an encephalocele defect.⁷

In the largest prospective PK and safety study of EVG in pregnancy, which included data on 26 live-born infants, congenital anomalies were reported in two infants: one infant with amniotic band syndrome, microcephaly, and intrauterine growth restriction and one infant with ulnar postaxial polydactyly (supernumerary digit).² In a retrospective report of 137 infants in the United States who were born to mothers who received EVG during pregnancy, two birth defects were noted: one case of hydronephrosis and one case of encephalocele. Two cases of intrauterine fetal demise among the 134 pregnancies also were included in this report.⁸

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 8 for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) <i>Trade Name</i>	Formulation	Dosing Recommendations ^a	Use in Pregnancy
<p>Elvitegravir (EVG)</p> <p>Note: As of October 2017, the single-drug formulation of EVG (Vitekta) is no longer available.</p> <p>(EVG/c/FTC/TAF) <i>Genvoya</i></p> <p>(EVG/c/FTC/TDF) <i>Stribild</i></p>	<p>EVG/c/FTC/TAF (Genvoya):</p> <ul style="list-style-type: none"> EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet <p>EVG/c/FTC/TDF (Stribild):</p> <ul style="list-style-type: none"> EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg tablet 	<p>Standard Adult Doses <i>Genvoya and Stribild:</i></p> <ul style="list-style-type: none"> One tablet once daily with food <p>Pregnancy <i>PKs in Pregnancy:</i></p> <ul style="list-style-type: none"> PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy. <p><i>Dosing in Pregnancy:</i></p> <ul style="list-style-type: none"> EVG plasma concentrations are reduced with use of standard adult doses during pregnancy; however, higher-than-standard doses of EVG have not been studied. Insufficient data are available to recommend a dose for use in pregnancy. <p>For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF).</p>	<p>Evidence of high placental transfer of EVG and low transfer of COBI.^b</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p> <p>EVG/c is not recommended for use in pregnancy. For women who become pregnant while taking EVG/c, consider frequent viral load monitoring or switching to a more effective, recommended regimen. If a woman continues taking a regimen that contains EVG/c, doses should be administered with a meal and should not be administered within 2 hours of ingesting any preparation that contains such minerals as iron or calcium, including prenatal vitamins.</p>

^a 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 10](#)).

^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: ARV = antiretroviral; COBI = cobicistat; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

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