Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from https://aidsinfo.nih.gov/guidelines on 9/13/2019

Elvitegravir (EVG)

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

There are insufficient human data on the use of elvitegravir during pregnancy to determine the drug-associated risk for birth defects and miscarriage.

Animal Studies

Carcinogenicity

Elvitegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in long-term studies in mice and rats at exposures up to 14-fold and in rats at exposures up to 27-fold that achieved with human systemic exposure at the recommended dose.[1]

Reproduction/Fertility

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures than those seen in humans receiving 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 elvitegravir.[1]

Placental and Breast Milk Passage

No data are available describing placental transfer of elvitegravir in nonhuman primates. Studies in rats have demonstrated that elvitegravir is secreted in breast milk.[1]

Human Studies in Pregnancy

Pharmacokinetics

A study with pharmacokinetic (PK) and safety data from 30 pregnant women with HIV who received a fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (TDF) has been published. Compared to postpartum, elvitegravir area under the curve (AUC) was 24% lower in the second trimester and 44% lower in the third trimester while elvitegravir trough concentration (C_{24}) was 81% lower in the second trimester and 89% lower in the third trimester. Cobicistat AUC was 54% to 57% lower and C_{24h} was 72% to 76% lower in the second and third trimesters compared with postpartum. Elvitegravir AUC failed to reach the exposure target of 23 mcg•hr/mL (the 10th percentile for nonpregnant adults) in 50% of women during the second trimester and 55% of women during the third trimester, compared with 12% of women postpartum. Plasma HIV RNA at delivery was less than 50 copies/mL in 19 of 25 women (76%) for whom data were available.[2] A smaller study of the PK of elvitegravir administered with cobicistat in seven pregnant women found reductions of 33% in AUC and 65% in C_{trough} during the third trimester compared with postpartum. One of the seven women had detectable plasma HIV RNA at delivery.[3] Two case reports of elvitegravir and cobicistat PK, safety, and efficacy in individual pregnant women found similar reductions in elvitegravir and cobicistat exposure during pregnancy although viral loads in both women remained undetectable throughout pregnancy.[4,5] One case report measured unbound elvitegravir concentrations and found an unbound fraction of 0.3% during pregnancy compared to 0.5% at 6 months postpartum.[5] In order to maximize absorption, elvitegravir should be administered with a meal and should not be administered within 2 hours of intake of preparations containing minerals such as iron or calcium, including prenatal vitamins.[6]

Placental and Breast Milk Passage

Placental passage of elvitegravir has been evaluated in three studies. The largest study of elvitegravir PK and safety observed that elvitegravir crossed the placenta well with a median cord to maternal plasma ratio of 91%. Median elvitegravir elimination half-life in neonates was 7.6 hours, similar to that in non-pregnant adults. Cobicistat concentrations were low in cord blood and were not detected in the plasma of any neonates.[2] Similar results were seen in the 2 smaller series of women from the United States and Europe and in several case reports.[4,5] No data are available on human breast milk transfer of elvitegravir.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to elvitegravir in humans have been monitored to be able to make a risk determination.[7] In the largest PK and safety study that 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 study of the safety and efficacy of the elvitegravir, cobicistat, emtricitabine, and TDF combination product in adult women with HIV, there were 10 infants born to the women in the study and none had birth defects.[8]

Excerpt from Table 10[a]

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
Elvitegravir (EVG) **Note:** As of October 2017, Vitekta (i.e., EVG as a single-entity formulation) is no longer available (EVG/COBI/FTC/TAF) *Genvoya* (EVG/COBI/FTC/TDF) *Stribild*	EVG/COBI/FTC/TAF (Genvoya): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg tablet EVG/COBI/FTC/TDF (Stribild): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg tablet	Standard Adult Dose (Genvoya and Stribild): • 1 tablet once daily with food Dosing in Pregnancy: • Insufficient data to make dosing recommendation PK in Pregnancy: • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy.	Evidence of high placental transfer of EVG and low transfer of COBI.[b] Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. EVG/COBI **is not recommended** for use in pregnancy. For women who become pregnant while taking EVG/c, consider switching to a more effective, recommended regimen. If an EVG/COBI regimen is continued, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.

[a] Individual ARV drug dosages 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—Mean or median cord blood/maternal delivery plasma drug ratio:

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

Key to Acronyms: COBI = cobicistat; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring

References

1. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203100s030lbl.pdf.
2. Momper J, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS. 2018. In Press.
3. Colbers A, Schalkwijk S, Konopnicki D, Rockstroh J, Burger D. Elvitegravir pharmacokinetics during pregnancy and postpartum. Abstract 17. Presented at: 19th International Workshop on Clinical Pharmacology of Antiviral Therapy. 2018. Baltimore, Maryland. Available at: http://www.natap.org/2018/Pharm/Pharm_11.htm.
4. Schalkwijk S, Colbers A, Konopnicki D, et al. First reported use of elvitegravir and cobicistat during pregnancy. *AIDS*. 2016;30(5):807-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26913711.
5. Marzolini C, Decosterd L, Winterfeld U, et al. Free and total plasma concentrations of elvitegravir/cobicistat during pregnancy and postpartum: a case report. *Br J Clin Pharmacol*. 2017;83(12):2835-2838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28512794.
6. Genvoya [package insert]. Food and Drug Administration. 2017. Available at: https://www.gilead.com/~/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf?la=en.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report

for 1 January 1989–31 January 2018. Wilmington, NC: Registry Coordinating Center. 2018. Available at: http://www.apregistry.com/.

8. Squires KE, Kityo C, Hodder S, et al. The safety and efficacy of E/C/F/TDF In treatment-naïve women with HIV-1 infection (WAVES Study): week 96 results. Presented at: 7th International Workshop on HIV & Women. 2017. Seattle, WA. Available at: http://regist2.virology-education.com/2017/7hivwomen/22_Squires.pdf.