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

Downloaded from https://aidsinfo.nih.gov/guidelines on 10/17/2018

Elvitegravir (Viteka, EVG)

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

There are insufficient human data on the use of elvitegravir in pregnancy to inform a drug-associated risk determination 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 at exposures up to 14-fold and 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 in humans at standard dosing. Fertility was normal in offspring.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Studies in rats and rabbits have shown no evidence of teratogenicity or effect on reproductive function with elvitegravir.[1]

Placental and Breast Milk Passage

No data on placental passage are available for elvitegravir. 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 29 pregnant women with HIV receiving a fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (TDF) has been presented. Elvitegravir area under the curve (AUC) was 43% to 50% lower and C24 was 86% to 87% lower in the second and third trimesters compared to levels in the same women postpartum. Cobicistat AUC was 54% to 57% lower and C24 was 72% to 76% lower in the second and third trimesters compared to levels in the same women postpartum. Elvitegravir AUC was below 23 mcg*hr/mL (the 10th percentile for nonpregnant adults) in 50% of women during the second trimester, 55% during the third trimester and 12% postpartum. Plasma HIV RNA at delivery was less than 50 copies/mL for 14 of the 19 women (74%) for whom data were available.[2] A case report of elvitegravir and cobicistat PK, safety, and efficacy in a single pregnant woman found similar reductions in elvitegravir and cobicistat exposure during pregnancy, including elvitegravir C_{min} below the suggested target concentration of 0.13 mg/L. Despite the low elvitegravir exposure in this woman, viral load remained undetectable throughout the pregnancy.[3]

Placental and Breast Milk Passage

A large study of elvitegravir PK and safety observed that elvitegravir crossed the placenta well and had an elimination half-life in neonates similar to that in non-pregnant adults. Cobicistat was not detected in the plasma of any neonates.[2] In the single case report cited above, maternal delivery and cord blood plasma elvitegravir concentrations were both 0.30 mg/L, while cobicistat was not detectable in maternal delivery and cord blood samples.[3] 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.[4] In the PK and safety study described above, congenital anomalies were reported in two of 26 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 study women and none had birth defects.[5]

Excerpt from Table 9[a]

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Elvitegravir (EVG) *Vitekta* **Note:** As of October 2017, Vitekta (i.e., EVG as a single-entity formulation) is no longer available **Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate** (EVG/COBI/ FTC/TDF) *Stribild* **Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide** (EVG/COBI/FTC/TAF) *Genvoya*	Tablet (Stribild): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg Tablet (Genvoya): • EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg	Standard Adult Dose (Stribild and Genvoya): • 1 tablet once daily with food. PK in Pregnancy: • PK studies in women who received EVG/c demonstrated significant reduction in EVG plasma exposure during pregnancy. Dosing in Pregnancy: • Insufficient data to make dosing recommendation.	Evidence of high placental transfer of EVG and low transfer of COBI. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits. . EVG/c **is not recommended** for initial use in pregnancy. For women who become pregnant while taking EVG/c, consider switching to a more effective, recommended regimen. If an EVG/c regimen is continued, viral load should be monitored frequently, and TDM (if available) may be useful.

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

Key to Acronyms: COBI = cobicistat; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; 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. Best B, Caparelli E, Stek A, et al. Elvitegravir/cobicistat pharmacokinetics in pregnancy and postpartum. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA.
3. 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.
4. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989–31 July 2016. Wilmington, NC: Registry Coordinating Center. 2016. Available at http://www.apregistry.com/.
5. Squires KE, Kityo C, Hodder S, et al. The safety and efficacy Of E/C/F/TDF in treatment-naive women with HIV-1 infection (WAVES Study): week 96 results. Presented at: 7th International Workshop on HIV & Women. 2017. Seattle, WA.