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



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## *Maraviroc (Selzentry, MVC)*

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

The limited data available on the use of maraviroc during pregnancy are not sufficient to assess any potential drug-associated risk of birth defects.

### Animal Studies

*Carcinogenicity*

Maraviroc was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of maraviroc in rats showed no drug-related increases in tumor incidence at exposures approximately 11 times those observed in humans at the therapeutic dose.

*Reproduction/Fertility*

Reproductive toxicity has been evaluated in rats and rabbits. Maraviroc produced no adverse effects on the fertility of male or female rats at doses with exposures (area under the curve [AUC]) up to 20-fold higher than those seen in humans given the recommended 300-mg, twice-daily dose.

*Teratogenicity/Adverse Pregnancy Outcomes*

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with maraviroc. During organogenesis in the rat and rabbit, systemic exposures (AUC) to maraviroc were approximately 20 times (in rats) and 5 times (in rabbits) the exposure seen in humans given the recommended 300-mg, twice-daily dose. In the rat prenatal and postnatal development study, maternal maraviroc AUC was approximately 14 times the exposure seen in humans given the recommended 300-mg, twice-daily dose.[1]

*Placental and Breast Milk Passage*

A study in rhesus macaques showed that single-dose maraviroc had poor placental transfer and rapid clearance from infant monkeys' blood.[2] Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.[1]

### Human Studies in Pregnancy

*Pharmacokinetics*

A U.S./European study of intensive, steady-state, 12-hour pharmacokinetic profiles in the third trimester, and at least 2 weeks postpartum, included 18 women taking maraviroc as part of clinical care.[3] Sixty-seven percent of the women in the study were taking maraviroc 150 mg BID with a protease inhibitor; 11% took maraviroc 300 mg BID and 22% took an alternative regimen. The geometric mean ratios for third-trimester AUC versus postpartum AUC were 0.72 and 0.70 for maximum maraviroc concentration. Despite an overall 30% decrease in maraviroc AUC during pregnancy and a 15% decrease in $C_{trough}$, $C_{trough}$ exceeded the minimum target concentration of 50 ng/mL in all participants except for one woman who had a $C_{trough}$ below 50 ng/mL during both pregnancy and postpartum. These data suggest that the standard adult dose adjusted for concomitant antiretroviral (ARV) drugs seems appropriate in pregnancy. A review of drug interactions between ARV drugs and oral contraceptives found that it is safe to co-administer oral contraceptives with maraviroc.[4]

*Placental and Breast Milk Passage*

An *ex vivo* human placental cotyledon perfusion model demonstrated minimal placental passage of maraviroc.[5] In a study in humans of six mother and infant pairs, the median ratio of cord blood to maternal plasma drug concentrations was 0.33 (0.03–0.56).[3,6] Whether maraviroc is secreted into human milk is unknown.

*Teratogenicity/Adverse Pregnancy Outcomes*

The 27 cases of first-trimester exposure that have been monitored to date in the Antiretroviral Pregnancy

Registry and other available first-trimester exposure data are insufficient to make a risk determination regarding birth defects.[7,8]

*Other Safety Information*

A retrospective study from an English-Irish cohort of 857 pregnant women showed an increased rate of hepatotoxicity among the 492 women who started ARV therapy during pregnancy.[9] Maraviroc was one of three drugs that was associated with an increased risk of liver enzyme elevation during pregnancy, with an aHR of 4.19 (1.34–13.1, $P = 0.01$), along with efavirenz and nevirapine. In a model using human placental BeWo cells, maraviroc inhibited transplacental passage of two fluorescent organic cations, suggesting that it might influence placental drug transfer and cause drug-drug interactions.[10]

**Excerpt from Table 10**[a]

| Generic Name (Abbreviation) *Trade Name* | Formulation | Dosing Recommendations | Use in Pregnancy |
|---|---|---|---|
| **Maraviroc** (MVC) *Selzentry* | MVC (Selzentry) *Tablets:* • 150 mg • 300 mg | Standard Adult Dose: • MVC 300 mg twice daily with or without food • MVC should only be used for patients with CCR5-tropic virus (and no X4-tropic virus). Dose Adjustments: • Increase to MVC 600 mg BID when used with potent CYP3A inducers: EFV, ETR, and rifampin. • Decrease to MVC 150 mg BID when used with CYP3A inhibitors: all PIs except TPV/r, itraconazole. PK in Pregnancy: • A PK study in human pregnancy demonstrated a 20% to 30% overall decrease in AUC, but $C_{trough}$ exceeded the recommended minimal concentration of 50 ng/mL. Dosing in Pregnancy: • Standard adult dosing adjusted for concomitant ARV use appears appropriate. | No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans. MVC placental passage category should be moderate.[b] |

[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 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 to Acronyms:** ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CYP3A = cytochrome P450 3A4; EFV = efavirenz; ETR = etravirine; MCV = maraviroc; PI = protease inhibitor; PK = pharmacokinetic; TPV/r = tipranavir/ritonavir

## References


1. Maraviroc [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208984_022128s017lbl.pdf.
2. Winters MA, Van Rompay KK, Kashuba AD, Shulman NS, Holodniy M. Maternal-fetal pharmacokinetics and dynamics of a single intrapartum dose of maraviroc in rhesus macaques. *Antimicrob Agents Chemother*. 2010;54(10):4059-4063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20696881.
3. Colbers A, Best B, Schalkwijk S, et al. Maraviroc pharmacokinetics in HIV-1-infected pregnant women. *Clin Infect Dis*. 2015;61(10):1582-1589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26202768.
4. Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. *Clin Pharmacokinet*. 2015;54(1):23-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25331712.
5. Vinot C, Gavard L, Treluyer JM, et al. Placental transfer of maraviroc in an *ex vivo* human cotyledon perfusion model and influence of ABC transporter expression. *Antimicrob Agents Chemother*. 2013;57(3):1415-1420. Available at: http://

www.ncbi.nlm.nih.gov/pubmed/23295922.

6. Colbers A, Best B, et al. A Comparison of the pharmacokinetics of maraviroc during pregnancy and postpartum. Abstract 931. Presented at: 20th Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, GA.
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. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001–2011. *BJOG*. 2013;120(12):1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721372.
9. Huntington S, Thorne C, Anderson J, et al. Does pregnancy increase the risk of ART-induced hepatotoxicity among HIV-positive women? *J Int AIDS Soc*. 2014;17(4 Suppl 3):19486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25393995.
10. Nabekura T, Kawasaki T, Kamiya Y, Uwai Y. Effects of antiviral drugs on organic anion transport in human placental BeWo cells. *Antimicrob Agents Chemother*. 2015;59(12):7666-7670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26416870.