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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Maraviroc (Selzentry, MVC)

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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 animal 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 fertility of male or female rats at doses with exposures (area under the curve [AUC]) up to 20-fold higher than 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 (area under the curve [AUC]) to maraviroc were approximately 20 times (in rats) and 5 times (in rabbits) the exposure in humans at the recommended 300-mg, twice-daily dose. In the rat prenatal and postnatal development study, maternal maraviroc AUC was approximately 14 times the exposure in humans at the recommended 300-mg, twice-daily dose.

Placental and Breast Milk Passage

Minimal placental passage was demonstrated in a study of single-dose maraviroc in rhesus macaques that showed poor placental transfer and rapid clearance from infant monkeys’ blood. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.

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. Sixty-seven percent were taking 150 mg BID with a protease inhibitor; 11% took 300 mg BID and 22% took an alternative regimen. The geometric mean ratios for third-trimester versus postpartum AUC were 0.72 and 0.70 for maximum maraviroc concentration. Despite the overall 30% decrease in maraviroc exposure during pregnancy and 15% decrease in C\textsubscript{trough}, C\textsubscript{trough} exceeded the minimum target concentration of 50 ng/mL, and only one woman had a C\textsubscript{trough} below that level both during 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 coadminister oral contraceptives with maraviroc.

Placental and Breast Milk Passage

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

Teratogenicity/Adverse Pregnancy Outcomes

The 26 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.
Other Safety Information

A retrospective study from an English-Irish cohort of 857 pregnant women showed an increased rate of hepatotoxicity among the 492 who started antiretroviral therapy during pregnancy. 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.\(^\text{10}\)

### Excerpt from Table 9\(^\text{a}\)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
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</table>
| **Maraviroc (MVC)** Selzentry | Tablets:  
• 150 mg  
• 300 mg | **Standard Adult Dose:**  
• 300 mg twice daily with or without food  
• Maraviroc should only be used for patients with CCR5-tropic virus (and no X4-tropic virus). | No evidence of teratogenicity in rats or rabbits; insufficient data to assess for teratogenicity in humans. MVC placental passage category should be moderate.\(^\text{b}\) |
|  |  | **Dose Adjustments:**  
• Increase to 600 mg BID when used with potent CYP3A inducers: EFV, ETR, and rifampin.  
• Decrease to 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 \( C_{\text{trough}} \) exceeded the recommended minimal concentration of 50 ng/mL. |  |
|  |  | **Dosing in Pregnancy:**  
• Standard adult dosing adjusted for concomitant ARV use appears appropriate. |  |

\(^{a}\) 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).

\(^{b}\) Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

**Key to Acronyms:** ARV = antiretroviral; AUC = area under the curve; BID = twice daily; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; PI = protease inhibitor; PK = pharmacokinetic

### References


