



**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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Etravirine (Intelence, ETR)

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

Etravirine is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.¹ Etravirine was evaluated for carcinogenic potential in mice and rats for up to approximately 104 weeks. Areas under the concentration-time curve (AUC) were 0.6-fold (mice) and 0.2-fold to 0.7-fold (rats) compared to human AUC due to intolerance of the formulation. In rats and male mice, no significant findings were noted. In female mice, increased incidences of hepatocellular carcinoma and of hepatocellular adenomas or carcinomas combined were seen. The relevance to humans of these liver tumor findings in mice is unknown.¹

Reproduction/Fertility

Etravirine had no effect on fertility and early embryonic development when tested in rats at maternal doses resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).¹

Teratogenicity/Adverse Pregnancy Outcomes

Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal toxicity or altered development.¹

Human Studies in Pregnancy

Pharmacokinetics

Etravirine pharmacokinetics (PK) in pregnant women have been reported in two studies. Ramgopal et al. found that total etravirine AUC, C_{\min} , and C_{\max} were increased approximately 1.1-fold to 1.4-fold in the second trimester (n = 13) and third trimester (n = 10) compared with levels in the same women postpartum (n = 10). Differences in unbound etravirine concentrations were less pronounced, with least-squares mean ratios of approximately 0.9 to 1.2.² Similarly, Mulligan et al. found increases by 1.3-fold to 1.9-fold in total etravirine AUC, C_{\min} , and C_{\max} during the third trimester (n = 13) compared with levels in the same women postpartum (n = 8).³ Etravirine was well tolerated in both of these studies.

Placental and Breast Milk Passage

The median (range) ratio of etravirine concentrations in cord blood-to-maternal-plasma at delivery in 7 mother-infant pairs was 0.52 (0.19–4.25).³ The median (range) cord blood-to-maternal concentrations in 10 mother-infant pairs in another study was 0.32 (0.19–0.63).² Placental passage of etravirine was described in a report of the use of etravirine, darunavir/ritonavir, and enfuvirtide in a woman who gave birth to twins, with cord blood etravirine levels of 414 ng/mL in Twin 1 and 345 ng/mL in Twin 2 (no maternal delivery etravirine concentration reported).⁴

In 8 women who began etravirine on postpartum day 1, plasma and breast milk concentrations were measured on postpartum days 5 and 14.⁵ Plasma PK were not different between days 5 and 14 and were similar to published PK parameters of etravirine in non-pregnant adults. Breast milk AUC₀₋₁₂ was higher in mature milk (Day 14) than in colostrum/transitional milk (Day 5): 12,954 ± 10,200 versus 4,372 ± 3,016 ng-h/mL (P = 0.046). Median etravirine concentrations in plasma and breast milk on Day 5 were 300 ng/mL and 241 ng/mL (within subject breast milk/plasma ratio of 109%). Median plasma and breast milk concentrations on day 14 were 197 ng/mL and 798 ng/mL (within-subject breast milk/plasma ratio of 327%). The maximum concentration in breast milk was significantly higher than in plasma (1,245 ± 1,159 vs. 531 ± 336 ng/mL, P = 0.04). Two women had detectable HIV RNA in breast milk on Day 14 despite suppressed plasma viral load. Etravirine concentrations in plasma and breast milk were similar in these two women compared to women with undetectable HIV RNA in breast milk. Etravirine penetrates well and may accumulate in breast milk.

Teratogenicity/**Adverse Pregnancy Outcomes**

In eight reported cases of etravirine use in pregnancy, no maternal, fetal, or neonatal toxicity was noted.^{4,6} One infant was born with a small accessory auricle on the right ear with no other malformations, but no birth defects were noted in the other children.⁴ **Among cases of first-trimester etravirine exposure reported to the Antiretroviral Pregnancy Registry, 1 defect has been noted in 60 live births; due to this low number of cases to date, no conclusions can be made about risk of birth defects.⁷**

Excerpt from **Table 9^a**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Etravirine (ETR) <i>Intence</i>	Tablets: • 25 mg • 100 mg • 200 mg For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	Standard Adult Dose(s): • 200 mg twice daily with food PK in Pregnancy: • PK data in pregnancy (n = 26) suggest 1.2–1.6-fold increased etravirine exposure during pregnancy. Dosing in Pregnancy: • No change in dose indicated.	Variable placental transfer, usually in the moderate to high categories, ranging from 0.19–4.25 (data from 19 mother-infant pairs). ^b Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

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

^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: ETR= etravirine; PK = pharmacokinetic

References

1. Etravirine [package insert]. Food and Drug Administration. 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022187s016lbl.pdf. Accessed September 22, 2017.
2. Ramgopal M, Osiyemi O, Zorrilla C, et al. Pharmacokinetics of total and unbound etravirine in HIV-1-infected pregnant women. *J Acquir Immune Defic Syndr*. 2016;73(3):268-274. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27159225>.
3. Mulligan N, Schalkwijk S, Best BM, et al. Etravirine pharmacokinetics in HIV-infected pregnant women. *Front Pharmacol*. 2016;7:239. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27540363>.
4. Furco A, Gosrani B, Nicholas S, et al. Successful use of darunavir, etravirine, enfuvirtide and tenofovir/emtricitabine in pregnant woman with multiclass HIV resistance. *AIDS*. 2009;23(3):434-435. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19188762>.
5. Spencer L, Liu S, Wang C, Neely M, Louie S, Kovacs A. Intensive etravirine PK and HIV-1 viral load in breast milk and plasma in HIV+ women receiving HAART. Poster 891. Conference on Retroviruses and Opportunistic Infections March 3-6 2014, 2014; Boston, MA.
6. Calcagno A, Trentini L, Marinaro L, et al. Transplacental passage of etravirine and maraviroc in a multidrug-experienced HIV-infected woman failing on darunavir-based HAART in late pregnancy. *J Antimicrob Chemother*. 2013;68(8):1938-1939. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23535879>.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–1 January 2016. Wilmington, NC: Registry Coordinating Center. 2016. Available at <http://www.apregistry.com/>.