



**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 December 7, 2018; last reviewed December 7, 2018)

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. Due to intolerance of the formulation, areas under the concentration-time curve (AUC) for etravirine were 0.6-fold (in mice) and 0.2-fold to 0.7-fold (in rats) compared to the typical AUC in humans receiving standard dosing. In rats and male mice, no significant findings were noted. In female mice, increased incidences of hepatocellular carcinoma and hepatocellular adenomas or carcinomas combined were seen. It is unclear whether these liver tumor findings in mice are relevant to humans.¹

Reproduction/Fertility

Etravirine had no effect on fertility and early embryonic development when tested in pregnant rats at doses that resulted in systemic drug exposures equivalent to those observed in humans who received the recommended dose (400 mg/day).¹

Teratogenicity/Adverse Pregnancy Outcomes

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

Human Studies in Pregnancy

Pharmacokinetics

Etravirine pharmacokinetics (PKs) 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 1.3-fold to 1.9-fold increases 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

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

Plasma and breast milk concentrations were measured on postpartum days 5 and 14 in eight women who began taking etravirine on postpartum day 1.⁵ Plasma PKs were similar between days 5 and 14 and were similar to published PK parameters of etravirine in nonpregnant adults. Etravirine AUC_{0-12h} in breast milk was higher in mature milk (Day 14) than in colostrum/transitional milk (Day 5): 12,954 ± 10,200 ng*h/mL 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, respectively (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 etravirine concentration in breast milk was significantly

higher than in plasma ($1,245 \pm 1,159$ ng/mL vs. 531 ± 336 ng/mL, $P = 0.04$). Two women had detectable HIV RNA in breast milk on Day 14 despite suppressed plasma viral loads. Etravirine concentrations in the plasma and breast milk of these women were similar to those observed in 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 but no other malformations, and no birth defects were noted in the other children.⁴ Among cases of first-trimester etravirine exposure reported to the Antiretroviral Pregnancy Registry, one defect has been noted out of 66 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 10^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Etravirine (ETR) <i>Intence</i>	<u>Tablets:</u> • 25 mg • 100 mg • 200 mg For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.	<u>Standard Adult Dose:</u> • 200 mg twice daily with food <u>PK in Pregnancy:</u> • PK data in pregnancy (n = 26) suggest that etravirine exposure during pregnancy increases 1.2-fold to 1.6-fold. <u>Dosing in Pregnancy:</u> • 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 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; ETR= etravirine; PK = pharmacokinetic

References

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