



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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Etravirine (Intelence, ETR)

(Last updated April 29, 2016; last reviewed April 29, 2016)

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 by oral gavage administration to mice and rats for up to approximately 104 weeks. Daily doses of 50, 200, and 400 mg/kg were administered to mice and doses of 70, 200, and 600 mg/kg were administered to rats in the initial period of approximately 41 to 52 weeks. The high and middle doses were subsequently adjusted because of tolerability and reduced by 50% in mice and by 50% to 66% in rats to allow for completion of the studies. In the mouse study, statistically significant increases in the incidences of hepatocellular carcinoma and of hepatocellular adenomas or carcinomas combined were observed in treated females. In the rat study, no statistically significant increases in tumor findings were observed in either sex. The relevance to humans of these liver tumor findings in mice is unknown. Because of tolerability of the formulation in these rodent studies, maximum systemic drug exposures achieved at the doses tested were lower than those in humans at the clinical dose (400 mg/day), with animal versus human area under the curve (AUC) ratios being 0.6-fold (mice) and 0.2- to 0.7-fold (rats).¹

Reproduction/Fertility

No effect on fertility and early embryonic development was observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).¹

Teratogenicity/Developmental Toxicity

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. Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1000 mg/kg/day). In both species, no treatment-related embryo-fetal effects (including malformations) were observed. In addition, no treatment effects were observed in a separate prenatal and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day).¹

Human Studies in Pregnancy

Pharmacokinetics

Etravirine pharmacokinetics (PK) in pregnant women have been reported in two studies. Ramgopal et al. found that AUC, C_{\min} , and C_{\max} were increased approximately 1.4 fold in the second trimester (n = 13) and 1.2 to 1.4 fold in the third trimester (n = 10) compared with the same women postpartum (n = 10).² Similarly, Best and colleagues found increases by 1.3 to 1.6 fold in AUC, C_{\min} , and C_{\max} during the third trimester (n = 13) compared with the same women postpartum (n = 9).³ Etravirine was well tolerated in both of these studies. Case report data are available describing etravirine use in a total of seven pregnant women.⁴ No adverse effects associated with etravirine use were reported. One report described etravirine PK in four pregnant women whose etravirine PK parameters were similar to those in non-pregnant adults.⁵

Placental and Breast Milk Passage

The median (range) ratio of etravirine concentrations in cord blood to maternal plasma at delivery in 6 mother-infant pairs was 0.76 (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 Etravirine concentrations in cord blood and maternal plasma at delivery were 112 ng/mL and 339 ng/mL, respectively (cord/maternal ratio of 33%), in one mother-infant pair.⁵ In a second mother-infant pair, cord blood and maternal plasma at delivery were 218 ng/

mL and 421 ng/mL (cord/maternal ratio of 51%).⁶ Placental passage of etravirine was described in a report of the use of etravirine, ritonavir-boosted darunavir, 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 14.⁷ 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/Developmental Toxicity

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 Fewer than 200 first-trimester pregnancy exposures have been reported to the Antiretroviral Pregnancy Registry; therefore, no conclusions can be made about risk of birth defects.⁸

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Names	Formulation	Dosing Recommendations	Use in Pregnancy
Etravirine (ETR) <i>Intence</i>	<p>Tablets:</p> <ul style="list-style-type: none"> • 25 mg • 100 mg • 200 mg <p>For patients unable to swallow tablets whole, the tablets may be dispersed in a glass of water.</p>	<p>Standard Adult Dose(s):</p> <ul style="list-style-type: none"> • 200 mg twice daily with food <p>PK in Pregnancy:</p> <ul style="list-style-type: none"> • PK data in pregnancy (n = 26) suggest 1.2–1.6 fold increased etravirine exposure during pregnancy. <p>Dosing in Pregnancy:</p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>Variable placental transfer, usually in the moderate to high categories, ranging from 0.19–4.25 (data from 18 mother-infant pairs).^b</p> <p>Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.</p>

^a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 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

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