



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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Raltegravir (Isentress, RAL)

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

According to the Food and Drug Administration, raltegravir has been evaluated in a limited number of women during pregnancy, and available human and animal data suggest that raltegravir does not increase the risk of major birth defects overall compared to the background rate.¹

Animal Studies

Carcinogenicity

Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential at systemic exposures 1.8-fold (females) or 1.2-fold (males) greater than human exposure at the recommended dose. Treatment-related squamous cell carcinoma of the nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir (exposure 3-fold higher than in humans at the recommended adult dose) for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats receiving doses resulting in systemic exposures that were 1.7-fold (males) to 1.4-fold (females) greater than the human exposure at the recommended dose.¹

Reproduction/Fertility

Raltegravir produced no adverse effects on fertility of male or female rats at doses up to 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended adult human dose).

Teratogenicity/Adverse Pregnancy Outcomes

Studies in rats and rabbits revealed no evidence of treatment-related effects on embryonic/fetal survival or fetal weights from raltegravir administered in doses producing systemic exposures approximately 3- to 4-fold higher than the exposure at the recommended adult human daily dose. In rabbits, no treatment-related external, visceral, or skeletal changes were observed. However, treatment-related increases in the incidence of supernumerary ribs were seen in rats given raltegravir at 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended human daily dose).¹

Placental and Breast Milk Passage

Placental transfer of raltegravir was demonstrated in both rats and rabbits. In rats given a maternal dose of 600 mg/kg/day, mean fetal blood concentrations were approximately 1.5- to 2.5-fold higher than in maternal plasma at 1 and 24 hours post-dose, respectively. However, in rabbits, the mean drug concentrations in fetal plasma were approximately 2% of the mean maternal plasma concentration at both 1 and 24 hours following a maternal dose of 1000 mg/kg/day.¹

Raltegravir is secreted in the milk of lactating rats, with mean drug concentrations in milk about 3-fold higher than in maternal plasma at a maternal dose of 600 mg/kg/day. No effects in rat offspring were attributable to raltegravir exposure through breast milk.¹

Human Studies

Pharmacokinetics

Raltegravir pharmacokinetics (PK) were evaluated in 42 women during pregnancy in the IMPAACT P1026s study. Raltegravir PKs in these women showed extensive variability as is also seen in non-pregnant individuals. Median raltegravir area under the curve (AUC) was reduced by approximately 50% during pregnancy. No significant difference was seen between the third trimester and postpartum trough concentrations. Plasma HIV RNA levels were under 400 copies/mL in 92% of women at delivery. Given the high rates of virologic suppression and the lack of clear relationship between raltegravir concentration and virologic effect in non-pregnant adults, no change in dosing was recommended during pregnancy.² In a study of 22 women with paired third-trimester and postpartum data from the PANNA Network, the geometric mean

ratios of third trimester/postpartum values were AUC_{0-12hr} 0.71 (0.53–0.96), C_{max} 0.82 (0.55–1.253), and C_{12hr} 0.64 (0.34–1.22). One patient was below the target C_{12hr} in the third trimester and none were below the threshold postpartum. No change in dosing during pregnancy was recommended based on these data.³

In a single-center observational study of pregnant women who were started on raltegravir as part of intensification of an antiretroviral (ARV) regimen or part of triple ARV regimens, the raltegravir C_{12h} in the second and third trimester were similar to historical data in non-pregnant population and the cord blood/maternal plasma concentration ratio was 1.03.⁴

In the P1097 study of washout PKs in 21 neonates born to women receiving ongoing raltegravir in pregnancy, raltegravir elimination was highly variable and extremely prolonged in some infants (median $t_{1/2}$ 26.6 hours; range 9.3–184 hours).³ In a case report of an infant born at 30 weeks' gestation after the mother had received 3 doses of raltegravir, the cord blood level of raltegravir was 145 ng/mL; the level at age 2 days was 106 ng/mL and at 1 month was 29 ng/mL, still above the IC95 of 15 ng/mL.⁵ In a report of 14 infants exposed to raltegravir *in utero*, the infants had no adverse effects and the raltegravir level had been within therapeutic range.⁶

Caution is advised when raltegravir is co-administered with atazanavir, a UGT1A1 inhibitor, because the combination results in elevated levels of raltegravir, based on a study in healthy, adult non-pregnant women.⁷

Placental and Breast Milk Passage

High bidirectional transfer of raltegravir across the placenta was demonstrated in an *ex vivo* study of term placentas from normal pregnancies and established that raltegravir crosses the placenta.⁸

***In vivo* human studies have confirmed** that raltegravir readily crosses the placenta. In the IMPAACT P1026s study, the ratio of cord blood-to-maternal-plasma was 1.5.² In the P1097 study, the median cord blood/maternal delivery plasma raltegravir concentration ratio was 1.48 (range 0.32–4.33), and in the PANNA study it was 1.21.^{3,9} Other case reports have shown cord blood/maternal blood drug level ratios of 1.00 to 1.06.^{10,11,12} In a series of 3 cases with preterm deliveries at 29 to 33 weeks' gestation (in 2 cases raltegravir was added to the maternal ARV regimen shortly before anticipated preterm delivery), cord blood-to-maternal-plasma ratios ranged from 0.44 to 1.88.¹³

Whether raltegravir is secreted in human breast milk is unknown.

Teratogenicity/Adverse Birth Outcomes

As of **January 31, 2017, seven** cases with defects have been reported among **263** infants with first-trimester exposure to raltegravir included in the Antiretroviral Pregnancy Registry. The prevalence of birth defects in exposed cases was **2.7 (95% CI, 1.1–5.4) compared with a 2.8 % total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.**¹⁴

Safety

In the P1026s Study and the PANNA study, raltegravir was well tolerated, with no treatment-related serious adverse events (AEs) in pregnant women, and all infants were at least 36 weeks' gestation at delivery.^{2,3} In multiple case reports and case series of 4, 5, and 14 pregnant women treated with raltegravir in combination with 2 or 3 other ARV drugs because of persistent viremia or late presentation, the drug was well tolerated and led to rapid reduction in HIV RNA levels.¹⁵⁻²¹

However, in 1 case report, 10- to 23-fold increases in maternal liver transaminases were reported after initiation of raltegravir with resolution when raltegravir was discontinued.²² Drug levels were not measured.

One case has been reported of drug reaction with eosinophilia and systemic symptoms syndrome with extensive pulmonary involvement in a postpartum woman that resolved with discontinuation of raltegravir. Such reactions have been reported in non-pregnant adults receiving raltegravir and should be considered in the differential diagnosis of fever during pregnancy or postpartum period in women on raltegravir.²³ In a study of 155 **non-pregnant** adults with HIV, mean age 49.2 years, who started on raltegravir-containing therapy, skeletal muscle toxicity frequency was 23.9% and isolated creatine kinase (CK) elevation was reported in 21.3%

(grade 1–2 and self-limiting); fewer than 3% of patients complained of myalgia or muscle weakness. Skeletal muscle toxicity and CK elevation were significantly associated with prior use of zidovudine, higher baseline CK levels, and a higher body mass index.²⁴

Because raltegravir is highly protein bound to albumin, there is concern about displacement of bilirubin from albumin in the neonate, potentially increasing the risk of neonatal hyperbilirubinemia. In an *in vitro* study of the effect of raltegravir on bilirubin-albumin binding, raltegravir had minimal effect on bilirubin-albumin binding at concentrations of 5 µM and 10 µM, caused a small but statistically significant increase in unbound bilirubin at 100 µM, and caused potentially harmful increases at 500 and 1000 µM.²⁵ These data suggest that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant at typical peak concentrations reached in adults with usual dosing (adult concentrations with standard raltegravir doses were geometric mean C_{max} of 4.5 µM, median C_{max} of 6.5 µM and maximum observed C_{max} of 10.2 µM).²⁵ In the P1097 study, one (4.6%) infant received phototherapy for treatment of hyperbilirubinemia, but this was judged not related to maternal raltegravir use.⁹ Raltegravir should not be used in neonates until PK and toxicity studies have been completed.^{9,25} In the P1097 study, no infant AEs were determined to be related to maternal raltegravir use.⁹

In a retrospective study of 31 pregnant women receiving raltegravir at a standard dose as part of a standard antiretroviral therapy regimen or as part of an intensification regimen late in pregnancy (median gestational age 34 weeks), mild elevation of transaminases in 35% of neonates was reported.²⁶

Chewable tablets contain phenylalanine.

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Raltegravir (RAL) <i>Isentress</i> Isentress HD	<u>Isentress</u> <i>Film-Coated Tablets:</i> • 400 mg <i>Chewable Tablets:</i> • 25 mg • 100 mg Isentress HD <i>Film-Coated Tablets:</i> • 600 mg	<u>Standard Adult Dose:</u> • 400-mg film-coated tablets twice daily without regard to food. • Two 600-mg film-coated (1200 mg) once daily for treatment-naïve patients or patients already virologically suppressed on initial regimen of RAL 400 mg BID without regard to food • Chewable and oral suspension doses are not interchangeable to either film-coated tablets or to each other. <u>With Rifampin:</u> • Two 400-mg film-coated tablets (800 mg) twice daily without regard to food. <u>PK in Pregnancy:</u> • Decreased levels in third trimester not of sufficient magnitude to warrant change in dosing. <u>Dosing in Pregnancy:</u> • No change in dose indicated. • Once-daily dosing (i.e., two 600-mg film-coated tablets) should not be used in pregnant women until more information is available.	High placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Case report of markedly elevated liver transaminases with use in late pregnancy. Severe, potentially life-threatening and fatal skin and hypersensitivity reactions have been reported in non-pregnant adults. Chewable tablets contain phenylalanine.

^a Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult and Adolescent Antiretroviral 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: PK = pharmacokinetic; RAL = raltegravir

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