



**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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Raltegravir (Isentress, RAL)

(Last updated December 7, 2018; last reviewed December 7, 2018)

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 (in females) or 1.2-fold (in 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 raltegravir 600 mg/kg/day for 104 weeks. This dose produced exposures that were three-fold higher than exposures seen in humans who received the recommended adult dose. 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 with systemic exposures that were 1.7-fold (in males) or 1.4-fold (in females) greater than the exposure observed in humans who received the recommended dose.¹

Reproduction/Fertility

Raltegravir produced no adverse effects on the fertility of male or female rats at doses up to 600 mg/kg/day, which provided exposures that were up to three-fold higher than the exposures seen in humans who received 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 that produced systemic exposures approximately three-fold to four-fold higher than the exposures seen in humans who received 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 (which produced exposures that were three-fold higher than the exposure seen in humans who received the recommended daily dose).¹

Placental and Breast Milk Passage

Placental transfer of raltegravir was demonstrated in both rats and rabbits. In pregnant rats given a dose of raltegravir 600 mg/kg/day, mean fetal blood concentrations were approximately 1.5-fold to 2.5-fold higher than the concentrations in maternal plasma at 1 hour and 24 hours post-dose, respectively. However, in rabbits, the mean drug concentration in fetal plasma was approximately 2% of the mean maternal plasma concentration at both 1 hour and 24 hours following a maternal dose of 1,000 mg/kg/day.¹

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

Human Studies in Pregnancy

Pharmacokinetics

Raltegravir pharmacokinetics (PK) were evaluated in 42 women during pregnancy in the IMPAACT P1026s study. Raltegravir PKs in these women showed extensive variability; variability is also seen in nonpregnant 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 a clear relationship between raltegravir concentration and

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virologic effect in nonpregnant 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 no patients 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_{12hr} in the second and third trimester were similar to historical data in a nonpregnant population, and the cord blood/maternal plasma raltegravir concentration ratio was 1.03.⁴

In the P1097 study of washout PKs in 21 neonates born to women who received ongoing raltegravir during 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 three 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 age 1 month the level was 29 ng/mL, still above the IC_{95} of 15 ng/mL.⁵ In a report of 14 infants who were exposed to raltegravir *in utero*, the infants had no adverse effects and raltegravir levels were within therapeutic range.⁶

Caution is advised when raltegravir is coadministered with atazanavir, a uridine diphosphate glucuronosyltransferase UGT1A1 inhibitor, because this combination results in elevated levels of raltegravir according to the results of a study in healthy, nonpregnant adult women.⁷

Placental and Breast Milk Passage

An *ex vivo* study of term placentas from normal pregnancies reported high bidirectional transfer of raltegravir across 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 raltegravir concentration was 1.5.² In the P1097 study, the median cord blood/maternal delivery plasma raltegravir concentration ratio was 1.48 (with a range of 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 1.06.¹⁰⁻¹² In a series of three cases with preterm deliveries at 29 to 33 weeks' gestation (in two of these 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 Pregnancy Outcomes

As of **January 31, 2018, nine** cases of birth defects have been reported among the **291** infants with first-trimester exposure to raltegravir that are included in the Antiretroviral Pregnancy Registry. The prevalence of birth defects among exposed infants was **3.09% (95% CI, 1.42–5.79)**, compared with a 2.8% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.^{14,15}

In a retrospective study of 497 women in the French Perinatal Cohort who received raltegravir during pregnancy, there were similar rates of birth defects among infants born to women who were on raltegravir in the first trimester and those born to women who initiated raltegravir in the second or third trimester (5.7% vs. 3.5%, $P = 0.29$). No specific pattern of birth defects emerged during the study.¹⁵

Safety

In the P1026s study and the PANNA study, raltegravir was well tolerated, with no treatment-related serious adverse events in pregnant women. All infants had reached a gestational age of ≥ 36 weeks at delivery.^{2,3} In multiple case reports and case series that involved four, five, and 14 pregnant women who were treated with raltegravir in combination with two or three other ARV drugs due to persistent viremia or late presentation, raltegravir was well tolerated and led to rapid reduction in HIV RNA levels.¹⁶⁻²²

However, in one case report, 10-fold to 23-fold increases in maternal liver transaminases were reported after

initiation of raltegravir. Resolution occurred when raltegravir was discontinued.²³ Drug levels were not measured.

One case of drug reaction has been reported with eosinophilia and systemic symptoms syndrome with extensive pulmonary involvement in a postpartum woman. The drug reaction resolved with discontinuation of raltegravir. Such reactions have been reported in nonpregnant adults receiving raltegravir, and these reactions should be taken into consideration when making a differential diagnosis of fever in women on raltegravir during pregnancy or the postpartum period.²⁴ In a study of 155 nonpregnant adults with HIV (mean age 49.2 years) who initiated raltegravir-containing therapy, skeletal muscle toxicity occurred in 23.9% of participants and isolated creatine kinase (CK) elevation was reported in 21.3% of participants. These instances of CK elevation were Grade 1 or 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.²⁵

Because raltegravir is highly protein bound to albumin, there is concern about displacement of bilirubin from albumin in the neonate, which could potentially increase 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 µM and 1,000 µM.²⁶ These data suggest that the effect of raltegravir on neonatal bilirubin binding is unlikely to be clinically significant at the typical peak concentrations reached in adults with the usual dosing (adult concentrations with standard raltegravir doses had a geometric mean C_{max} of 4.5 µM, a median C_{max} of 6.5 µM, and a maximum observed C_{max} of 10.2 µM).²⁶ In the P1097 study, one of 19 infants (5.3%) received phototherapy for treatment of hyperbilirubinemia, but this was judged to be unrelated to maternal raltegravir use.⁹ In a retrospective study of 31 pregnant women who received a standard dose of raltegravir as part of a standard antiretroviral therapy regimen or as part of an intensification regimen late in pregnancy (at a median gestational age of 34 weeks), mild elevation of transaminases in 35% of neonates was reported.²⁷

Raltegravir chewable tablets contain phenylalanine.

Excerpt from Table 10^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Raltegravir (RAL) <i>Isentress</i> <i>Isentress HD</i>	<u>RAL (Isentress)</u> <i>Film-Coated Tablets:</i> • 400 mg <i>Chewable Tablets:</i> • 25 mg • 100 mg <u>RAL (Isentress HD)</u> <i>Film-Coated Tablets:</i> • 600 mg	<u>Standard Adult Doses:</u> • RAL 400-mg, film-coated tablets twice daily without regard to food • Two RAL 600-mg, film-coated tablets (1200 mg) once daily for ARV-naïve patients or patients who are already virologically suppressed on an initial regimen of RAL 400 mg twice daily without regard to food • Chewable and oral suspension doses are not interchangeable with either film-coated tablets or each other <u>With Rifampin:</u> • Two RAL 400-mg, film-coated tablets (800 mg) twice daily without regard to food <u>PK in Pregnancy:</u> • Decreased drug concentrations in third trimester not of sufficient magnitude to warrant a change in dosing. <u>Dosing in Pregnancy:</u> • No change in dose is indicated. • Once-daily dosing (i.e., two RAL 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 RAL use in late pregnancy. Severe, potentially life-threatening, and fatal skin and HSRs have been reported in nonpregnant adults. Chewable tablets contain phenylalanine. To maximize RAL absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.

Excerpt from Table 10^a

^a Individual ARV drug doses 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; **BIC = bictegravir**; **HSR = hypersensitivity reaction**; PK = pharmacokinetic; RAL = raltegravir

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