

Raltegravir (Isentress, RAL)

(Last updated October 26, 2016; last reviewed October 26, 2016)

Raltegravir is classified as Food and Drug Administration Pregnancy Category C.

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.¶

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/Developmental Toxicity

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).¶

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.¶

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.¶

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 pharmacokinetics (PK) 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).⁸ 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 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

Teratogenicity/Developmental Toxicity

As of July 31, 2015, six cases with defects have been reported among 192 infants with first-trimester exposure to raltegravir included in the Antiretroviral Pregnancy Registry—too few first-trimester exposures to be able to accurately calculate the prevalence of birth defects in exposed cases.⁷

Placental and Breast Milk Passage

In humans, raltegravir appears to readily cross 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.^{3,8} Other case reports have shown cord blood/maternal blood drug level ratios of 1.00 to 1.06.^{9,10,11} In a series of three 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 1.88.¹²

Whether raltegravir is secreted in human breast milk is unknown.

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 the P1097 study, no infant AEs were determined to be related to maternal raltegravir exposure; one (4.6%) infant received phototherapy for treatment of hyperbilirubinemia.⁸ 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.¹³⁻¹⁸ However, in one case of similar use, 10- to 23-fold increases in maternal liver transaminases were reported after initiation of raltegravir with resolution when raltegravir was discontinued.¹⁹ Drug levels were not measured in any of those studies. 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.²⁰ In a study of 155 adult HIV-infected adults, mean age 49.2 years, 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.²¹

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 .²² 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).²² Raltegravir should not be used in neonates until PK and toxicity studies have been completed.⁸

Chewable tablets contain phenylalanine.

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Raltegravir (RAL) Isentress	<p><u>Film-Coated Tablets:</u></p> <ul style="list-style-type: none"> • 400 mg <p><u>Chewable Tablets:</u></p> <ul style="list-style-type: none"> • 25 mg • 100 mg 	<p><u>Standard Adult Dose:</u></p> <ul style="list-style-type: none"> • 400-mg film-coated tablets twice daily without regard to food. • Chewable and oral suspension doses are not interchangeable to either film-coated tablets or to each other. <p><u>With Rifampin:</u></p> <ul style="list-style-type: none"> • 800-mg film-coated tablets twice daily without regard to food. <p><u>PK in Pregnancy:</u></p> <ul style="list-style-type: none"> • Decreased levels in third trimester not of sufficient magnitude to warrant change in dosing. <p><u>Dosing in Pregnancy:</u></p> <ul style="list-style-type: none"> • No change in dose indicated. 	<p>High placental transfer to fetus.^b</p> <p>Insufficient data to assess for teratogenicity in humans. Increased skeletal variants in rats, no increase in defects in rabbits.</p> <p>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.</p> <p>Chewable tablets contain phenylalanine.</p>

^a Individual antiretroviral 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 Abbreviations: PK = pharmacokinetic; RAL = raltegravir

References

1. Raltegravir [package insert]. Food and Drug Administration. 2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022145s035.203045s012.205786s0031bl.pdf. Accessed September 23, 2016.
2. Watts DH, Stek A, Best BM, et al. Raltegravir pharmacokinetics during pregnancy. *J Acquir Immune Defic Syndr*. 2014;67(4):375-381. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25162818>.
3. Blonk M, Colbers A, Hidalgo-Tenorio C, et al. Raltegravir in HIV-1 infected pregnant women: pharmacokinetics, safety and efficacy. *Clin Infect Dis*. 2015. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25944344>.
4. Belissa E, Benchikh A, Charpentier C, et al. Raltegravir plasma concentrations in HIV-1 infected pregnant women. Presented at: Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, WA.
5. Clavel-Osorio C, Cazassus F, Stegmann S, Huc-Anais P, Lecam D, Peytavin G. One-month transplacental pharmacokinetics of raltegravir in a premature newborn after short-course treatment of the HIV-1-infected mother. *Antimicrob Agents Chemother*. 2013;57(12):6393-6394. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24080650>.
6. Trahan MJ, Lamarre V, Metras ME, Lapointe N, Kakkar F. Raltegravir for the prevention of mother-to-child transmission of HIV. Presented at: International AIDS Society. 2015. Vancouver, CA.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 July 2015. Wilmington, NC: Registry Coordinating Center. 2015. Available at <http://www.apregistry.com/>.

8. Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir Immune Defic Syndr*. 2014;67(3):310-315. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25162819>.
9. Pinnetti C, Baroncelli S, Villani P, et al. Rapid HIV-RNA decline following addition of raltegravir and tenofovir to ongoing highly active antiretroviral therapy in a woman presenting with high-level HIV viraemia at week 38 of pregnancy. *J Antimicrob Chemother*. 2010;65(9):2050-2052. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20630894>.
10. Croci L, Trezzi M, Allegri MP, et al. Pharmacokinetic and safety of raltegravir in pregnancy. *Eur J Clin Pharmacol*. 2012. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22382989>.
11. McKeown DA, Rosenvinge M, Donaghy S, et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. *AIDS*. 2010;24(15):2416-2418. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20827058>.
12. Hegazi A, Mc Keown D, Doerholt K, Donaghy S, Sadiq ST, Hay P. Raltegravir in the prevention of mother-to-child transmission of HIV-1: effective transplacental transfer and delayed plasma clearance observed in preterm neonates. *AIDS*. 2012;26(18):2421-2423. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23151500>.
13. Taylor N, Touzeau V, Geit M, et al. Raltegravir in pregnancy: a case series presentation. *Int J STD AIDS*. 2011;22(6):358-360. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21680678>.
14. Cha A, Shaikh R, Williams S, Berkowitz LL. Rapid reduction in HIV viral load in late pregnancy with raltegravir: a case report. *Journal of the International Association of Providers of AIDS Care*. 2013;12(5):312-314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23695227>.
15. De Hoffer L, Di Biagio A, Bruzzone B, et al. Use of raltegravir in a late presenter HIV-1 woman in advanced gestational age: case report and literature review. *Journal of Chemotherapy*. 2013;25(3):181-183. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23783144>.
16. Westling K, Pettersson K, Kaldma A, Naver L. Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. *AIDS Patient Care STDS*. 2012;26(12):714-717. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23101466>.
17. Nobrega I, Travassos AG, Haguihara T, Amorim F, Brites C. Short communication: Use of raltegravir in late-presenting HIV-infected pregnant women. *AIDS Res Hum Retroviruses*. 2013;29(11):1451-1454. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23731224>.
18. Adeyemo A, Wood C, Govind A. Achieving rapid reduction of HIV-1 viral load in HIV-positive pregnant women close to term - an obstetric/medical emergency: a review of three cases. *Int J STD AIDS*. 2013;24(7):591-592. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23970779>.
19. Renet S, Closon A, Brochet MS, Bussieres JF, Boucher M. Increase in Transaminase Levels Following the Use of Raltegravir in a Woman With a High HIV Viral Load at 35 Weeks of Pregnancy. *JOGC*. 2013;35(1):68-72. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23343800>.
20. Yee BE, Nguyen NH, Lee D. Extensive pulmonary involvement with raltegravir-induced DRESS syndrome in a postpartum woman with HIV. *BMJ Case Reports*. 2014;2014. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24798353>.
21. Calza L, Danese I, Colangeli V, et al. Skeletal muscle toxicity in HIV-1-infected patients treated with a raltegravir-containing antiretroviral therapy: a cohort study. *AIDS Res Hum Retroviruses*. 2014;30(12):1162-1169. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25369244>.
22. Clarke DF, Wong RJ, Wenning L, Stephenson DK, Mirochnick M. Raltegravir in vitro effect on bilirubin binding. *Pediatr Infect Dis J*. 2013. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23470680>.