Raltegravir (Isentress, RAL)

(Last updated January 17, 2020; last reviewed January 17, 2020)

Animal Studies

Carcinogenicity

Raltegravir (RAL) was neither mutagenic nor clastogenic in a series of in vitro and animal in vivo screening tests. Long-term carcinogenicity studies of RAL in mice did not show any carcinogenic potential at systemic exposures that were 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 RAL 600 mg/kg per 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 of RAL.

Reproduction/Fertility

RAL had no adverse effects on the fertility of male or female rats at doses up to 600 mg/kg per day, which produced exposures that were up to three-fold higher than the exposures seen in humans who received the recommended adult dose.

Teratogenicity/Adverse Pregnancy Outcomes

No treatment-related effects on embryonic/fetal survival or fetal weights were observed in studies where RAL was administered to rats and rabbits at doses that produced systemic exposures approximately three-fold to four-fold higher than the exposures seen in humans who received the recommended 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 RAL 600 mg/kg per day (which produced exposures that were three-fold higher than the exposure seen in humans who received the recommended daily dose).

Placental and Breast Milk Passage

Placental transfer of RAL was demonstrated in both rats and rabbits. In pregnant rats given a dose of RAL 600 mg/kg per 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 after a maternal dose of 1,000 mg/kg per day. RAL is secreted in the milk of lactating rats. At a maternal dose of RAL 600 mg/kg per day, the mean drug concentration in milk was about three-fold higher than the mean drug concentration in maternal plasma. No effects in rat offspring were attributable to RAL exposure through breast milk.

Human Studies in Pregnancy

Pharmacokinetics

RAL pharmacokinetics (PKs) were evaluated in 42 pregnant women in the IMPAACT P1026s study. RAL PKs in pregnant women showed extensive variability that was similar to the variability seen in nonpregnant women. Median RAL area under the curve (AUC) was reduced by approximately 50% during pregnancy. No significant difference was seen between third-trimester trough concentrations and postpartum trough concentrations. Plasma HIV RNA levels were <400 copies/mL in 92% of women at delivery. Given the high rates of virologic suppression and the lack of a clear relationship between RAL concentration and virologic effect in nonpregnant adults, no change in dosing was recommended during pregnancy. 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 0.71 for AUC_{0-12h} (range 0.53–0.96), 0.82 for C_{max} (range 0.55–1.253), and 0.64 for C_{12h} (range 0.34–1.22). One patient was below the target C_{12h} in the third trimester, and no patients were below the threshold postpartum. No change in dosing during pregnancy was recommended based on these data.
In a single-center, observational study of pregnant women who were started on RAL as part of intensification of an antiretroviral (ARV) regimen or as part of a triple-ARV regimen, the RAL C12h in the second and third trimester were similar to historical data in a nonpregnant population, and the cord blood-to-maternal-plasma RAL concentration ratio was 1.03.4

In the P1097 study of washout PKs in 21 neonates born to women who received RAL during pregnancy, RAL elimination was highly variable and extremely prolonged in some infants (median t1/2 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 RAL, the cord blood level of RAL was 145 ng/mL; the level at 2 days of age was 106 ng/mL, and at 1 month of age the level was 29 ng/mL, still above the IC95 of 15 ng/mL.5 In a report on 14 infants who were exposed to RAL in utero, the infants experienced no adverse effects and RAL levels were within therapeutic range.6

Caution is advised when RAL is coadministered with atazanavir, a uridine diphosphate glucuronosyltransferase 1A1 inhibitor, because this combination results in elevated levels of RAL according to the results of a study in nonpregnant adult women with no medical conditions.7

Placental and Breast Milk Passage

An ex vivo study of term placentas from normal pregnancies reported high bidirectional transfer of RAL across the placenta.8

In vivo human studies have confirmed that RAL readily crosses the placenta. In the IMPAACT P1026s study, the ratio of cord blood to maternal plasma RAL concentrations was 1.5.2 In the P1097 study, the median ratio of cord blood to maternal delivery plasma RAL concentrations 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-to-maternal-blood drug level ratios of 1.00 to 1.06.10-12 In three cases of preterm delivery at 29 to 33 weeks gestation (in two of these cases, RAL 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 RAL is secreted in human breast milk is unknown.

Teratogenicity/Adverse Pregnancy Outcomes

As of January 31, 2019, nine cases of birth defects have been reported among the 327 infants with first-trimester exposure to RAL that are included in the Antiretroviral Pregnancy Registry. The prevalence of birth defects among infants who were exposed to RAL was 2.75% (95% confidence interval [CI], 1.27–5.16), 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 RAL during pregnancy, there were similar rates of birth defects among infants born to women who were on RAL during the first trimester and those born to women who initiated RAL 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 Merck reviewed data on 456 periconception exposures to RAL and found no instances of neural tube defects; this review included data from the Merck company database, the Antiretroviral Pregnancy Registry, and the U.K./Ireland and French pregnancy cohorts.16

Safety

IMPAACT P1081 randomized 408 antiretroviral therapy-naive women in South America, Africa, Thailand, and the United States who presented late in pregnancy to receive RAL plus two nucleoside reverse transcriptase inhibitors (NRTIs) or efavirenz plus two NRTIs. Both regimens were well tolerated, with similar rates of stillbirth and preterm birth among women and similar rates of serious adverse events among women and infants.17

In the P1026s study and the PANNA study, RAL was well tolerated, with no treatment-related serious adverse events observed 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 RAL in combination with two or three other ARV drugs due to persistent viremia or late presentation, RAL was well tolerated and led to rapid reduction in HIV RNA levels.2,3,6,7,9-12
However, in one case report, 10-fold to 23-fold increases in maternal liver transaminase levels were reported after initiation of RAL. Resolution occurred when RAL was discontinued.\textsuperscript{25} Drug levels were not measured.

One case of drug reaction has been reported in a postpartum woman with eosinophilia and systemic symptoms syndrome with extensive pulmonary involvement. The drug reaction resolved with discontinuation of RAL. Such reactions have been reported in nonpregnant adults who were receiving RAL, and these reactions should be taken into consideration when making a differential diagnosis of fever in women on RAL during pregnancy or the postpartum period.\textsuperscript{26} In a study of 155 nonpregnant adults with HIV (mean age 49.2 years) who initiated RAL-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.\textsuperscript{27}

Because RAL 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 \textit{in vitro} study, RAL 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.\textsuperscript{28} These data suggest that the effect of RAL on neonatal bilirubin binding is unlikely to be clinically significant at the typical peak concentrations that are reached in adults who receive the recommended dose (adult concentrations with standard RAL doses had a geometric mean C\textsubscript{max} of 4.5 µM, a median C\textsubscript{max} of 6.5 µM, and a maximum observed C\textsubscript{max} of 10.2 µM).\textsuperscript{28} 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 RAL use.\textsuperscript{9} In a retrospective study of 31 pregnant women who received a standard dose of RAL as part of a standard ARV regimen or as part of an intensification regimen late in pregnancy (at a median gestational age of 34 weeks), mild elevation of transaminase levels was reported in 35\% of neonates.\textsuperscript{29}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Generic Name (Abbreviation) Trade Name} & \textbf{Formulation} & \textbf{Dosing Recommendations\textsuperscript{a}} \\
\hline
\textbf{Raltegravir (RAL)} \textbf{Isentress} \textbf{Isentress HD} & RAL (Isentress) Film-Coated Tablets: & \textbf{Standard Adult Doses} \\
& \textbullet 400 mg Chewable Tablets: & \textit{In Patients Who Are Not Receiving Rifampin:} \\
& \textbullet 25 mg & \textbullet RAL 400-mg, film-coated tablets twice daily without regard to food \\
& \textbullet 100 mg & \textbullet Two RAL 600-mg, film-coated tablets (1,200 mg) once daily \textit{without regard to food for ARV-naive patients or patients who are already virologically suppressed on an initial regimen of RAL 400 mg twice daily} \\
RAL (Isentress HD) Film-Coated Tablets: & & \textbullet Chewable tablets and oral suspension doses are not interchangeable with either film-coated tablets or each other. \\
& \textbullet 600 mg & \textit{In Patients Who Are Receiving Rifampin:} \\
& & \textbullet Two RAL 400-mg, film-coated tablets (800 mg) twice daily \textit{without regard to food} \\
& & \textbf{Pregnancy} \\
& & \textit{PKs in Pregnancy:} \\
& & \textbullet Decreased drug concentrations in third trimester are not of sufficient magnitude to warrant a change in dosing. \\
& & \textit{Dosing in Pregnancy:} \\
& & \textbullet No change in dose is indicated. \\
& & \textbullet Once-daily dosing (i.e., two RAL 600-mg, film-coated tablets) should not be used in pregnant women until more information is available. \\
& & \textbf{Use in Pregnancy} \\
& & High placental transfer to fetus.\textsuperscript{b} \\
& & No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). \\
& & There is a 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. \\
& & RAL 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. \\
\hline
\end{tabular}
\end{table}

\textit{Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States} G-102

Downloaded from https://aidsinfo.nih.gov/guidelines on 4/28/2020
Excerpt from Table 8

1. Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

2. 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: ARV = antiretroviral; HD = high dose; HSR = hypersensitivity reaction; PK = pharmacokinetic; RAL = raltegravir

References


