Raltegravir (Isentress, Isentress HD, RAL)

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Summary

- No dose adjustments are required for raltegravir (RAL) during pregnancy. There are no pharmacokinetic (PK) data to support use of daily RAL high dose (HD) during pregnancy at this time.
- First-trimester exposure to RAL is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

Three PK studies found third-trimester RAL exposure was commensurate with postpartum levels. The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1026s study, a Phase IV prospective PK study of selected antiretroviral (ARV) drugs during pregnancy and postpartum, evaluated the PK of RAL 400 mg twice daily in 42 pregnant women. RAL PK during pregnancy showed extensive variability that was similar to the variability seen in nonpregnant individuals. Median RAL area under the curve (AUC) was reduced by approximately 50% during pregnancy. No significant difference was seen in trough concentrations between the third trimester and postpartum. Plasma HIV RNA levels were <400 copies/mL in 92% of women at birth. 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.[1] In a study of 22 women on RAL 400 mg twice daily with paired third-trimester and postpartum data from the PANNA Network, a network of European centers that collect PK data on the use of newly developed ARV agents for HIV during pregnancy, the geometric mean ratios (GMRs) of third-trimester and postpartum values were 0.71 for AUC from 0 to 12 hours post-dose (90% confidence interval [CI], 0.53–0.96), 0.82 for maximum concentration (C_{max}) (range 0.55–1.253), and 0.64 for concentration 12 hours post-dose (C_{12h}) (range 0.34–1.22). One woman was below the target C_{12h} in the third trimester, and none were below the threshold postpartum. No change in dosing during pregnancy was recommended based on these data.[2] Most recently, a Brazilian PK study of RAL elimination among pregnant and postpartum women on RAL 400 mg twice daily (third trimester [n = 15], birth [n = 15], and postpartum data [n = 8]) also found similar RAL plasma exposure in the third trimester and postpartum.[3]

A population PK model of once-daily 1,200-mg RAL pooled 11 PK studies (n = 221), with the primary target for efficacy set as the lower bound of the 90% CI of the trough concentration >0.75. The simulated trough GMR for once-daily 1,200-mg RAL was 0.51 (90% CI, 0.41–0.63), falling below the primary target for efficacy and supporting the current recommendation against daily RAL dosing in pregnancy.[4]

Caution is advised when RAL is coadministered with atazanavir, a uridine diphosphate glucuronosyltransferase A1 inhibitor, because this combination can result in elevated levels of RAL in nonpregnant adults with no medical conditions.[5]

Placental and Breast Milk Passage

An *ex vivo* study of term placentas from normal pregnancies reported high bidirectional transfer of RAL across the placenta.[6]

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.[1] In the P1097 study, the median ratio of cord blood–to–maternal delivery plasma RAL concentrations was 1.48 (range 0.32–4.33), and in the PANNA study, it was 1.21.[2,7] In the above-mentioned single-center observational study of pregnant women who were started on RAL as part of intensification of an ARV regimen or as part of a triple-ARV regimen, the cord blood–to–maternal plasma RAL concentration ratio was 1.03.[8] Other case reports have shown cord blood–to–maternal blood drug level ratios of 1.00 to 1.06.[9-11] In three cases of preterm birth at 29 to 33 weeks gestation (in two of these cases, RAL was added to the maternal ARV regimen shortly before anticipated preterm birth), cord blood–to–maternal plasma ratios ranged from 0.44 to 1.88.[12]

Limited data indicate that maternal doses of up to 1,200 mg daily of RAL are transferred at low levels in breast milk and are not expected to cause any adverse effects in breastfed infants.[13] A small Swiss cohort found the median milk-to-plasma ratio was 0.96 for once-daily RAL and 0.39 for twice-daily RAL.[14] A single case study demonstrated low RAL transfer into breast milk and little accumulation.[15]

Teratogenicity/Adverse Pregnancy Outcomes

In a retrospective study of 703 women in the French Perinatal Cohort who received RAL during pregnancy, rates of birth defects among infants born to women who were on RAL at conception were slightly higher than those born to women who initiated RAL later in pregnancy (6.4% vs. 2.3%, $P = 0.04$). When compared with matched controls, RAL exposure at conception was not associated significantly with birth defects, and no specific pattern of birth defects emerged during the study. No differences in other perinatal outcomes between the groups were observed.[16] Merck reviewed data on 456 periconception exposures to RAL and found no instances of neural tube defects; this review included data from the Merck database, the Antiretroviral Pregnancy Registry, and the U.K./Ireland and French pregnancy cohorts.[17] A review of 1,499 pregnancies from nine cohorts within the European Pregnancy and Paediatric Infections Cohort Collaboration found an overall prevalence of birth defects of 3.9% (95% CI, 2.9–5.0), without an observed increase among pregnancies exposed to RAL periconception ($P = 0.29$). The proportion of preterm birth, low birth weight, and small for gestational age infants born to this population of women receiving RAL was not increased compared to large cohorts of pregnant women living with HIV; there were no observed differences in outcomes by timing of RAL exposure during pregnancy.[18]

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for RAL and other ARV drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to RAL to detect at least a twofold increase in the risk of overall birth defects, but no such increase has been observed. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to RAL and other ARV drugs reported to the APR where there are sufficient data to determine 95% CI. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention's surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 5.07 per 100 live births).

The IMPAACT P1081 study randomized 408 women in Africa, South America, Thailand, and the United States who had never used antiretroviral therapy and 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; a significantly larger proportion of women on a RAL-containing regimen achieved a viral load less than 200 copies/mL at or near birth.[19] In multiple case reports and case series that involved 4, 5, and 14 pregnant women who were treated with RAL in combination with two or three other ARV drugs because of persistent viremia or late presentation, RAL was well tolerated and led to rapid reduction in HIV RNA levels.[20-26]

Safety

In the P1026s study, P1081 study, and PANNA study, RAL was well tolerated, with no treatment-related serious adverse events observed in pregnant women.[1,2,19] 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.[27] 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 patients on RAL during pregnancy or the postpartum period.[28] 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 associated significantly with prior use of zidovudine, higher baseline CK levels, and a higher body mass index.[29]

Because RAL is highly protein bound to albumin, concern exists about displacement of bilirubin from albumin in the neonate, which potentially could increase the risk of neonatal hyperbilirubinemia. In an *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.[30] 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_{max} of 4.5 µM, a median C_{max} of 6.5 µM, and a maximum observed C_{max} of 10.2 µM).[30] In the P1097 study, 1 of 19 infants (5.3%) received phototherapy for treatment of hyperbilirubinemia, but this was judged to be unrelated to maternal RAL use.[7] 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.[31]

Animal Studies

Carcinogenicity

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.[32]

Reproduction/Fertility

RAL had no adverse effects on the fertility of male or female rats at exposures up to threefold 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 in which RAL was administered to rats and rabbits at doses that produced systemic exposures approximately threefold to fourfold 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 with RAL exposures that were threefold higher than the exposure seen in humans who received the recommended daily dose.[32]

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.[32]

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 threefold higher than the mean drug concentration in maternal plasma. No effects in rat offspring were attributable to RAL exposure through breast milk.[32]

Excerpt From Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Raltegravir (RAL) *Isentress* *Isentress HD*	**RAL (Isentress)** *Film-Coated Tablet* • 400 mg *Chewable Tablets* • 25 mg • 100 mg **RAL (Isentress HD)** *Film-Coated Tablet* • 600 mg	**Pregnancy** *PK in Pregnancy* • Decreased drug concentrations in the third trimester are not of sufficient magnitude to warrant a change in dosing. *Dosing in Pregnancy* • No change in dose is indicated. • Once-daily dosing (i.e., two RAL 600-mg film-coated tablets) **should not be used** during pregnancy until more information is available. **Standard Adult Doses** *In Patients Who Are Not Receiving Rifampin* • RAL 400-mg film-coated tablets twice daily without regard to food • Two RAL 600-mg film-coated tablets (1,200 mg) once daily without regard to food for patients who are ARV-naive or patients who are already virologically suppressed on an initial regimen of RAL 400 mg twice daily • Chewable tablets and oral suspension doses **are not interchangeable** with either film-coated tablets or each other. *In Patients Who Are Receiving Rifampin* • Two RAL 400-mg film-coated tablets (800 mg) twice daily without regard to food	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out a 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 reactions 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. **Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with RAL is contraindicated.

[a] 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).

[b] Placental transfer categories are determined by mean or median cord blood–to–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 = pharmacokinetics; RAL = raltegravir

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