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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Integrase Inhibitors

This class of antiretroviral (ARV) drugs inhibits integrase, the viral enzyme that catalyzes the two-step process of insertion of HIV DNA into the genome of the human cell. Integrase catalyzes a preparatory step that excises two nucleotides from one strand at both ends of the HIV DNA and a final “strand transfer” step that inserts the viral DNA into the exposed regions of cellular DNA. The integrase inhibitor drug class targets this second step in the integration process. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects reverse transcription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV that is resistant to other classes of ARV drugs.

Dolutegravir (Tivicay, DTG)

Dolutegravir is classified as Food and Drug Administration Pregnancy Category B.

Animal Carcinogenicity Studies

Dolutegravir was not genotoxic or mutagenic in vitro. No carcinogenicity was detected in 2-year long-term studies in mice at exposures up to 14-fold higher than that achieved with human systemic exposure at the recommended dose, or in rats at exposures up to 10-fold higher in males and 15-fold higher in females than human exposure at the recommended dose.

Reproduction/Fertility

Dolutegravir did not affect fertility in male and female rats and rabbits at exposures approximately 27-fold higher than human clinical exposure, based on area under the curve, at the recommended dose.

Animal Teratogenicity/Developmental Toxicity

Studies in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity or effect on reproductive function with dolutegravir.

Placental and Breast Milk Passage

Studies in rats have demonstrated that dolutegravir crosses the placenta in animal studies and is excreted into breast milk in rats.

Human Studies in Pregnancy

No studies of dolutegravir use in human pregnancy have been reported. No human data on placental passage or breast milk excretion are available.

Glossary of Terms for Supplement

<table>
<thead>
<tr>
<th>Term</th>
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<tr>
<td>Carcinogenic</td>
<td>producing or tending to produce cancer</td>
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<tr>
<td>Clastogenic</td>
<td>causing disruption of or breakages in chromosomes</td>
</tr>
<tr>
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<tr>
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<tr>
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Carcinogenic = producing or tending to produce cancer
• Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
• Genetic mutations and/or chromosomal damage can contribute to cancer formation.

Clastogenic = causing disruption of or breakages in chromosomes

Genotoxic = damaging to genetic material such as DNA and chromosomes

Mutagenic = inducing or capable of inducing genetic mutation

Teratogenic = interfering with fetal development and resulting in birth defects
**Elvitegravir**

*(Last updated August 6, 2015; last reviewed August 6, 2015)*

Elvitegravir is classified as Food and Drug Administration Pregnancy Category B.

**Animal Studies**

*Carcinogenicity*

Elvitegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in long-term studies in mice at exposures up to 14-fold and rats at exposures up to 27-fold that achieved with human systemic exposure at the recommended dose.1

*Reproduction/Fertility*

Elvitegravir did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures than in humans at standard dosing. Fertility was normal in offspring.1

*Teratogenicity/Developmental Toxicity*

Studies in rats and rabbits have shown no evidence of teratogenicity or effect on reproductive function with elvitegravir.1

**Placental and Breast Milk Passage**

No data on placental passage are available for elvitegravir. Studies in rats have demonstrated that elvitegravir is secreted in breast milk.

**Human Studies in Pregnancy**

*Pharmacokinetics*

No pharmacokinetic studies of elvitegravir in human pregnancy have been reported.

**Placental and Breast Milk Passage**

No data are available on placental or breast milk passage of elvitegravir in humans.

**Teratogenicity/Developmental Toxicity**

In the Antiretroviral Pregnancy Registry, insufficient numbers of first-trimester exposures to elvitegravir in humans have been monitored to be able to make a risk determination.2

**References**


**Raltegravir (Isentress, RAL)**

*(Last updated August 6, 2015; last reviewed August 6, 2015)*

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 seen in non-pregnant individuals. Median raltegravir area under the curve 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.1 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.²

In the P1097 study of washout pharmacokinetics in 21 neonates born to women receiving ongoing raltegravir in pregnancy, raltegravir elimination was highly variable and extremely prolonged in some infants (median t1/2 26.6 hours, range 9.3–184 hours). 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.³

Teratogenicity/Developmental Toxicity

As of January 31, 2015, six cases with defects have been reported among 180 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.⁴

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 1.5.¹ 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 1.21.²,³ Other case reports have shown cord blood/maternal blood drug level ratios of 1.00 to 1.06.⁶,⁷,⁸ In a series of three cases with preterm deliveries at 29 to 33 weeks’ gestation (in 2 cases raltegravir was added to the maternal antiretroviral regimen shortly before anticipated preterm delivery), cord blood-to-maternal-plasma ratios ranged from 0.44 to 1.88.⁹

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 in pregnant women, and all infants were at least 36 weeks’ gestation at delivery.¹,² In the P1097 study, no infant adverse events were determined to be related to maternal raltegravir exposure; one (4.6%) infant received phototherapy for treatment of hyperbilirubinemia.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 antiretroviral drugs because of persistent viremia or late presentation, the drug was well tolerated and led to rapid reduction in HIV RNA levels.¹⁰-¹⁵ However, in one case of similar use, 10- to 23-fold increases in liver transaminases were reported after initiation of raltegravir with resolution when raltegravir was discontinued.¹⁶ 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.¹⁷

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.¹⁸ 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 Cmax of 4.5 µM, median Cmax of 6.5 µM and maximum observed Cmax of 10.2 µM).¹⁸ Raltegravir should not be used in neonates until PK and toxicity studies have been completed.

Chewable tablets contain phenylalanine.

References


