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

Glossary of Terms for Supplement
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

One drug has been approved in this new class of antiretroviral (ARV) drugs aimed at inhibiting integrase, the viral enzyme that catalyzes the two-step process of insertion of HIV DNA into the genome of the host 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 retrotranscription 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.

Raltegravir (Isentress) is classified as Food and Drug Administration Pregnancy Category C.
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- Animal carcinogenicity studies
  Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of raltegravir are ongoing.

- Reproduction/fertility animal studies
  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 animal studies
  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. In humans, raltegravir appears to readily cross the placenta. In P1026s, maternal and cord blood from six deliveries of mothers receiving raltegravir-based therapy during pregnancy were evaluated; the ratio of cord blood to maternal plasma was 0.98 (95% confidence interval, 0.09–2.26).[1] Other case reports have shown similarly high cord blood/maternal blood drug level ratios of 1.00 to 1.06.[2, 3] In a report of three pregnant women with multiresistant HIV-1 who were given raltegravir in late pregnancy to rapidly reduce maternal viral load, raltegravir concentrations within 3 hours of delivery in the neonates of two patients were approximately 7 and 9.5 times higher than in the mother's paired sample; in the third infant, maternal plasma was not available but neonatal concentration was still high 2.5 hours after delivery.[4] However, no adverse reactions were observed in mothers or infants. 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. Whether raltegravir is secreted in human milk is unknown.

- Human studies in pregnancy
  Only limited data exist on the use of raltegravir in pregnancy. Raltegravir pharmacokinetics (PKs) were evaluated in 10 women in the IMPAACT P1026s study. Raltegravir PKs showed extensive variability but did not appear to be consistently altered during the third trimester compared with postpartum and historical data in non-pregnant individuals; thus the standard dose appears appropriate in pregnancy.[1] In a case series of 5 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.[5] Drug levels were not measured in that study.

References

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