



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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Rilpivirine (Edurant, RPV)

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

Animal Studies

Carcinogenicity

Rilpivirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Rilpivirine was not carcinogenic in rats when administered at doses 3 times higher than exposure in humans at the recommended dose of 25 mg once daily. Hepatocellular neoplasms were observed in both male and female mice at doses 21 times that of human therapeutic exposure; the observed hepatocellular findings in mice may be rodent-specific.¹

Reproduction/Fertility

No effect on fertility was observed when rilpivirine was tested in rats at maternal doses up to 400 mg/kg/day, resulting in systemic drug exposure equivalent to 40 times the recommended human dose.¹

Teratogenicity/Developmental Toxicity

No evidence of embryonic or fetal toxicity or an effect on reproductive function was observed in rat and rabbit dams treated with rilpivirine during pregnancy and lactation at doses 15 and 70 times higher, respectively, than exposure in humans at the recommended dose of 25 mg once daily.¹

Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that rilpivirine is present in rat milk.¹

Human Studies in Pregnancy

Pharmacokinetics

A case report describing rilpivirine pharmacokinetic (PK) evaluations at 32 weeks' gestation and again postpartum in 2 HIV-infected pregnant women showed that rilpivirine area under the curve [AUC] was decreased by 30% to 43% during pregnancy, while postpartum AUC was similar to that seen in non-pregnant adults.² A similar finding was reported in a study presenting PK and safety data from 32 HIV-infected pregnant women receiving rilpivirine. Median rilpivirine AUC and trough concentrations were reduced by about 20% to 30% in the second and third trimesters, compared with postpartum. Median trough rilpivirine concentrations were significantly lower at 14 visits where the women had detectable HIV-1 RNA (30 ng/mL) compared to 62 visits with undetectable HIV-1 RNA (63 ng/mL). Ninety percent of women had trough concentrations above the protein-adjusted EC₉₀ for rilpivirine. PK exposure was highly variable in this study.³

Placental and Breast Milk Passage

In the case report described above, cord blood and maternal plasma rilpivirine concentrations obtained from one mother-infant pair were 0.016 and 0.021 mg/L, for a cord blood/maternal concentration ratio of 0.74.² The PK and safety study described above included rilpivirine delivery concentration data from 9 mother-infant pairs, with median (range) cord blood rilpivirine plasma concentration of 53.8 ng/mL (<10.0 to 219.7 ng/mL), maternal delivery plasma rilpivirine concentration of 103.3 ng/mL (<10.0 to 273.4 ng/mL) and cord blood/maternal plasma ratio of 0.55 (0.38 to 0.83).⁴ An *ex vivo* human cotyledon perfusion model also showed that rilpivirine crosses the placenta with fetal transfer rates ranging from 17% to 37%.^{5,6} No data exist on whether rilpivirine is excreted in breast milk in humans.

Teratogenicity/Developmental Toxicity

The number of first-trimester exposures to rilpivirine that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.⁷

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Rilpivirine (RPV) Edurant (RPV/TDF/FTC) Complera	RPV (Edurant) Tablets: • 25 mg Complera: • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet	<u>Standard Adult Dose</u> RPV (Edurant): • 25 mg once daily with food Complera: • 1 tablet once daily with food <u>PK in Pregnancy:</u> • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 30% in pregnancy compared with postpartum, but most pregnant women exceeded target exposure. <u>Dosing in Pregnancy:</u> • Routine dosing adjustment in all women is not recommended for RPV during pregnancy. Individual patients should be closely monitored.	Moderate to high placental transfer to fetus. ^b No evidence of teratogenicity in rats or rabbits. Insufficient data to assess for teratogenicity in humans.

^a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult 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 Acronyms: AUC = area under the curve; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

References

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