

Rilpivirine (Edurant, RPV)

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Animal Studies

Carcinogenicity

Rilpivirine (RPV) was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* screening tests. RPV was not carcinogenic in rats when administered at doses that resulted in drug exposures that were three times higher than those seen in humans who received the recommended 25-mg dose of RPV once daily. Hepatocellular neoplasms were observed in both male and female mice at doses that produced exposures 21 times higher than human therapeutic exposure; however, whether these hepatocellular findings in mice are relevant to humans is unclear.¹

Reproduction/Fertility

No effect on fertility was observed when RPV was administered to rats at a dose of 400 mg/kg per day, which produced systemic drug exposure that was 40 times the exposure seen in humans who received the recommended dose.¹

Teratogenicity/Adverse Pregnancy Outcomes

Rat and rabbit dams treated with RPV during pregnancy showed no evidence of embryonic or fetal toxicity, and reproductive function was unaffected. RPV exposures were 15 times higher (in rats) and 70 times higher (in rabbits) than the exposures observed in humans who received the recommended dose of RPV 25 mg once daily. When rats were administered RPV 400 mg/kg per day through lactation, no drug-related adverse effects were seen in the offspring.¹

Placental and Breast Milk Passage

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

Human Studies in Pregnancy

Pharmacokinetics

A study that presented pharmacokinetic (PK) and safety data from 32 pregnant women with HIV found that median RPV area under the curve (AUC) and trough concentrations were about 20% to 30% lower in the second and third trimesters than in the postpartum period. Median trough RPV concentrations were significantly lower at 14 visits where the women had detectable HIV RNA (30 ng/mL) than at 62 visits where they had undetectable HIV RNA (63 ng/mL). Ninety percent of women had trough concentrations above the protein-adjusted EC₉₀ for RPV. PK parameters between participants were highly variable in this study.² Another study in 16 pregnant women with HIV similarly found that exposure was approximately 50% lower in the third trimester than in the postpartum period, with 4 of the 16 women having troughs below the target levels during pregnancy.³ Schalkwijk et al. recommended the use of therapeutic drug monitoring during the third trimester.³ Furthermore, they recommended that providers remind patients to take RPV doses with meals. A third study reported that total RPV exposure decreased by approximately 30%, and unbound RPV levels decreased by 22% to 25% during pregnancy in 15 women compared with the RPV exposures seen in the same women postpartum.⁴ Cervicovaginal fluid RPV concentrations were described in a study of 24 women who took RPV daily during pregnancy and postpartum. RPV steady-state concentrations in the cervicovaginal fluid of these women were similar to the concentrations seen in their plasma. The RPV cervicovaginal fluid-to-plasma AUC ratio was higher during pregnancy than postpartum.⁵ Although RPV plasma concentration is reduced during pregnancy, higher-than-standard doses of RPV have not been studied, and not enough data are available to recommend a dosing change during pregnancy. In the ANRS-EPF French Perinatal Cohort, 184 virologically suppressed women who switched to RPV-free regimens during pregnancy had a higher risk of viral rebound compared with 63 women who continued RPV during pregnancy (20% vs. 0%, $P = 0.046$). Delivery outcomes

were similar between groups.⁶ For considerations regarding switching antiretroviral drugs during pregnancy, see [Pregnant Women with HIV Who Are Currently Receiving Antiretroviral Therapy](#). Pregnant women who receive the standard dose of RPV should have their viral loads monitored more frequently than women who are not receiving RPV (see [Monitoring of the Woman and Fetus During Pregnancy](#)).

Placental and Breast Milk Passage

One of the PK and safety studies described above included data on RPV concentration at delivery for 21 mother–infant pairs, with a median cord blood RPV plasma concentration of 29.2 ng/mL (range <10.0 to 101.5 ng/mL), a median maternal delivery plasma RPV concentration of 55.2 ng/mL (range <10.0 to 233.8 ng/mL), and a median cord blood-to-maternal-plasma ratio of 0.55 (range 0.3–0.8).² Osiyemi et al. found that the median ratio of cord blood-to-maternal-plasma concentration of total RPV in eight women was 0.55 (range 0.43–0.98).⁴ Similarly, Schalkwijk et al. found a median cord blood-to-maternal-plasma ratio of 0.5 (range 0.35–0.81) in five women.³ An *ex vivo* human cotyledon perfusion model also showed that RPV crosses the placenta, with fetal transfer rates ranging from 17% to 37%.^{7,8} No data exist on whether RPV is excreted in breast milk in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry had monitored sufficient numbers of first-trimester exposures to RPV to detect at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with RPV. Among the cases of first-trimester exposures to RPV that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 1.4% (7 infants out of 495 live births; 95% confidence interval, 0.6% to 2.9%) compared with a 2.7% total prevalence in the U.S. population, according to Centers for Disease Control and Prevention surveillance.⁹

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of the individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) <i>Trade Name</i>	Formulation	Dosing Recommendations ^a	Use in Pregnancy
<p>Rilpivirine (RPV) <i>Edurant</i></p> <p>(RPV/FTC/TDF) <i>Complera</i></p> <p>(RPV/DTG) <i>Juluca</i></p> <p>(RPV/FTC/TAF) <i>Odefsey</i></p>	<p>RPV (Edurant) <i>Tablets:</i></p> <ul style="list-style-type: none"> • 25 mg <p>RPV/FTC/TDF (Complera):</p> <ul style="list-style-type: none"> • RPV 25 mg/ FTC 200 mg/ TDF 300 mg tablet <p>RPV/DTG (Juluca):</p> <ul style="list-style-type: none"> • RPV 25 mg/ DTG 50 mg tablet <p>RPV/FTC/TAF (Odefsey):</p> <ul style="list-style-type: none"> • RPV 25 mg/ FTC 200 mg/ TAF 25 mg tablet 	<p>Standard Adult Doses</p> <p><i>RPV (Edurant):</i></p> <ul style="list-style-type: none"> • RPV 25 mg once daily with a meal <p><i>RPV/FTC/TDF (Complera):</i></p> <ul style="list-style-type: none"> • One tablet once daily with a meal <p><i>RPV/DTG (Juluca):</i></p> <ul style="list-style-type: none"> • One tablet once daily with a meal <p><i>RPV/FTC/TAF (Odefsey):</i></p> <ul style="list-style-type: none"> • One tablet once daily with a meal <p>Pregnancy</p> <p><i>PKs in Pregnancy:</i></p> <ul style="list-style-type: none"> • RPV PKs are highly variable during pregnancy. RPV AUC and trough concentrations are 20% to 50% lower in pregnancy than postpartum. Although most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. <p><i>Dosing in Pregnancy:</i></p> <ul style="list-style-type: none"> • Although RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied, and not enough data are available to recommend a dosing change during pregnancy. Pregnant women receiving standard dosing should have their viral loads monitored more frequently than women who are not receiving RPV. <p>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., DTG, FTC, TAF, TDF).</p>	<p>Moderate-to-high placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out twofold increase in overall birth defects).</p> <p>Two-drug regimens (e.g., the RPV/DTG FDC) are not recommended for use in pregnancy.</p>

^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, Table 10](#)).

^b 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; AUC = area under the curve; DTG = dolutegravir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

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