## Rilpivirine (Edurant, RPV)

Updated: January 31, 2024
Reviewed: January 31, 2024

### *Summary*

- Rilpivirine (RPV) plasma concentrations after oral dosing are decreased by approximately 20% to 50% during pregnancy.
- Higher-than-standard oral doses have not been studied, and not enough data are available to recommend a dosing change during pregnancy. Pregnant individuals receiving standard oral dosing should have their viral loads monitored more frequently than individuals who are not receiving RPV.
- Pharmacokinetic data are insufficient to make dosing recommendations for long-acting injectable RPV during pregnancy or breastfeeding.
- First-trimester exposure to RPV is not associated with increased risk of congenital anomalies.

### *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 concentration (AUC) and trough concentration ($C_{trough}$) after oral dosing were about 20% to 30% lower in the second and third trimesters than in the postpartum period. Median RPV $C_{trough}$ 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 $C_{trough}$ above the protein-adjusted 90% maximal effective concentration ($EC_{90}$) for RPV. PK parameters between participants were highly variable in this study.[1]

Another study in 16 pregnant women with HIV similarly found that exposure after oral dosing was approximately 50% lower in the third trimester than in the postpartum period, with 4 of the 16 women having $C_{trough}$ below the target levels during pregnancy.[2] Schalkwijk et al. recommended the use of therapeutic drug monitoring during the third trimester.[2] Furthermore, they recommended that providers remind patients to take RPV doses with meals. A third study reported that total RPV exposure after oral dosing 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.[3]

Cervicovaginal fluid RPV concentrations were described in a study of 24 women who took RPV orally 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.[4] 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 these groups.[5] For considerations regarding switching antiretroviral drugs during pregnancy, see People With HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant. Pregnant people who receive the standard oral dose of RPV should have their viral loads monitored more frequently than people who are not receiving RPV (see Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy).

No studies have been conducted on the PKs of ongoing intramuscular injections of long-acting cabotegravir (CAB) and RPV during pregnancy. Clinical trial data reported to date are limited to pregnant women who stopped receiving the long-acting injectable formulations for the treatment or prevention of HIV once pregnancies were recognized and began alternative oral antiretroviral regimens throughout the remainder of their pregnancies. From the Phase 2b/3/3b clinical trials of long-acting injectable CAB and RPV for the treatment of HIV, PK data are available for seven of the nine participants with live birth outcomes. Plasma concentrations were within the range of observed concentrations of nonpregnant women who discontinued long-acting injectable CAB and RPV.[6] A physiologically-based PK model of pregnant individuals initiating long-acting injectable CAB and RPV early in the second trimester predicted a reduction in plasma concentrations of 29.5% and 23.0%, respectively, at the first trough after the first injection. After the sixth injection in the second and third trimesters, plasma concentrations were 31.1% and 29.2% lower for CAB and RPV, respectively. These reductions are attributable to the predicted induction of uridine diphosphate glucuronosyltransferase 1A1 and cytochrome P450 3A4 during the second and third trimesters.[7]

See Cabotegravir for data about CAB.

### 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 RPV plasma 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).[1] 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).[3] Similarly, Schalkwijk et al. found a median cord blood–to–maternal plasma ratio of 0.5 (range: 0.35–0.81) in five women.[2] An *ex vivo* human cotyledon perfusion model also showed that RPV crosses the placenta,[8,9] with fetal transfer rates ranging from 17% to 37%. No data exist on whether RPV is excreted in breast milk in humans.

### Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry monitored sufficient numbers of first-trimester exposures to oral 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 2.1% (14 infants out of 668 live births; 95% confidence interval, 1.2% to 3.5%) compared with a 2.7% total prevalence in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[10]

In the Phase 2b/3/3b trials of long-acting injectable CAB and RPV, 25 of 325 women of reproductive potential became pregnant while exposed to CAB and RPV (5 oral, 20 long-acting injectable),

resulting in 8 elective abortions, 6 spontaneous abortions (5 in the first trimester), 1 ectopic pregnancy, and 10 live births (1 oral, 9 long-acting injectable). Of the 10, there was 1 congenital ptosis in a term infant with intrauterine growth restriction and 1 late preterm delivery due to induction of labor.[6]

## *Animal Studies*

### Carcinogenicity

RPV was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* screening tests. RPV was neither carcinogenic nor genotoxic in animal studies.[11]

### Reproduction/Fertility

RPV had no effect on fertility in animal studies.[11]

### Teratogenicity/Adverse Pregnancy Outcomes

No significant toxicological effects were seen in RPV animal studies.[11]

### Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that RPV is present in rat milk.[11]

**Excerpt from Table 14**

**Note:** When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

| Generic Name (Abbreviation) *Trade Name* | Formulation | Dosing Recommendations[a] | Use in Pregnancy |
|---|---|---|---|
| Rilpivirine (RPV) *Edurant*<br><br>(RPV/FTC/TDF) *Complera*<br><br>(RPV/DTG) *Juluca*<br><br>(RPV/FTC/TAF) *Odefsey*<br><br>(CAB and RPV) *Cabenuva*<br><br>CAB and RPV is a two-drug co-packaged product for IM injection. | RPV (Edurant)<br><br>*Tablets*<br><br>• 25 mg<br><br>RPV/FTC/TDF (Complera)<br><br>• RPV 25-mg/ FTC 200-mg/ TDF 300-mg tablet<br><br>RPV/DTG (Juluca)<br><br>• RPV 25-mg/DTG 50-mg tablet<br><br>RPV/FTC/TAF (Odefsey)<br><br>• RPV 25-mg/FTC 200-mg/ TAF 25-mg tablet<br><br>CAB and RPV (Cabenuva)<br><br>• CAB 200-mg/mL suspension for IM injection<br><br>• RPV 300-mg/mL suspension for IM injection | Pregnancy<br><br>*PKs in Pregnancy*<br><br>• 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.<br><br>*Dosing in Pregnancy*<br><br>• 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 people receiving standard dosing should have their viral loads monitored more frequently than people who are not receiving RPV.<br><br>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (CAB, DTG, FTC, TAF, TDF).<br><br>Standard Adult Doses<br><br>*RPV (Edurant)*<br><br>• RPV 25 mg once daily with food | Moderate-to-high placental transfer to fetus[b]<br><br>No evidence of human teratogenicity (can rule out twofold increase in overall birth defects)<br><br>Two-drug regimens (e.g., the RPV/DTG FDC) are not recommended for use in pregnancy. |

## Excerpt from Table 14

| Generic Name (Abbreviation) *Trade Name* | Formulation | Dosing Recommendations[a] | Use in Pregnancy |
|---|---|---|---|
| | | *RPV/FTC/TDF (Complera)*<br>• One tablet once daily with food<br>*RPV/DTG (Juluca)*<br>• One tablet once daily with food<br>*RPV/FTC/TAF (Odefsey)*<br>• One tablet once daily with food<br>*CAB and RPV (Cabenuva)*<br>• Refer to Cabotegravir for dosing and instructions. | |

[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 12).

[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; AUC = area under the curve; CAB = cabotegravir; DTG = dolutegravir; FDC = fixed-dose combination; FTC = emtricitabine; IM = intramuscular; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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