

Rilpivirine (Edurant, RPV)

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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. When standard oral dosing of RPV is received during pregnancy, viral loads should be monitored more frequently.
- 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 an increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

RPV exposure after oral dosing is decreased by 20% to 50% during pregnancy. The International Maternal Pediatric Adolescent AIDS Clinical Trials P1026s (IMPAACT P1026) study evaluated pharmacokinetic (PK) and safety data from 32 pregnant women with HIV and found that median RPV area under the curve concentration (AUC) and trough concentration (C_{trough}) after oral dosing were approximately 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 for RPV. PK parameters between participants were highly variable in this study.¹ A subsequent study among 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 Based on these findings, the authors recommended therapeutic drug monitoring during the third trimester and oral RPV dosing with meals. A third study among 15 women during pregnancy reported that total RPV exposure after oral dosing decreased by approximately 30%, and unbound RPV levels decreased by 22% to 25% compared to their postpartum concentrations.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 virally 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%, $P = 0.046$). Birth outcomes were similar between these groups.⁵ For considerations regarding switching antiretroviral (ARV) drugs during pregnancy, see [When Antiretroviral Therapy is Being Taken When Pregnancy Occurs](#). When the standard oral dose of RPV is received during pregnancy, viral loads should be monitored more frequently (see [Initial Evaluation and Continued Monitoring of HIV During Pregnancy](#)).

No studies have been conducted on the PKs of ongoing intramuscular injections of long-acting cabotegravir (CAB) and RPV (LA CAB/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 ARV regimens throughout the remainder of their pregnancies. From the Phase 2b/3/3b clinical trials of LA CAB/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 LA CAB/RPV.⁶ A physiologically-based pharmacokinetics (PBPK) model of LA CAB/RPV initiation during pregnancy early in the second trimester predicted a reduction in RPV plasma concentrations of 23.0% at the first trough (C_{trough}) after the first injection. After the sixth injection in the second and third trimesters, plasma RPV concentrations were 29.2% lower. These reductions are attributable to the predicted induction of uridine diphosphate glucuronosyltransferase 1A1 and cytochrome P450 3A4 during the second and third trimesters.⁷ An additional publication by the same team simulated the monthly and bimonthly dosing regimens and predicted that C_{trough} at Week 12 for monthly and bimonthly long-acting RPV would fall below 50 ng/mL in at least 40% (for monthly dosing) and over 90% (for bimonthly dosing) among pregnant women. The predicted median cord-to-maternal blood ratio was 0.88 (range 0.78–0.93) for RPV between 38 and 40 weeks of gestation.⁸ A single case report of bimonthly LA CAB/RPV found that RPV concentrations were 70% to 75% lower than historical nonpregnant levels; viral suppression was maintained.⁹

See [Cabotegravir](#) for data about CAB.

Placental and Breast Milk Passage

RPV has moderate-to-high placental transfer compared to other ARV drugs. IMPAACT P1026 included data on RPV concentration at birth for 21 mother–infant pairs, with a median cord blood RPV plasma concentration of 29.2 ng/mL (range <10.0 ng/mL to 101.5 ng/mL), a median maternal delivery RPV plasma concentration of 55.2 ng/mL (range <10.0 ng/mL 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.^{2,10} No data exist on whether RPV is excreted in breast milk in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for RPV and other ARV drugs twice a year through an [interim report](#) released in June and December. The APR has 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. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the [APR interim report](#) provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to RPV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) according to the Centers for Disease Control and Prevention’s surveillance system (The Metropolitan Atlanta Congenital Defects Program or MACDP) and with the Texas Birth Defects Registry ([TBDR] 5.07 per 100 live births).

In the Phase 2b/3/3b trials of LA CAB/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 birth 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) <i>Edurant</i> (RPV/FTC/TDF) <i>Complera</i> (RPV/DTG) <i>Juluca</i> (RPV/FTC/TAF) <i>Odefsey</i> (CAB and RPV) <i>Cabenuva</i> Note: CAB and RPV is a two-drug copackaged product for IM injection. Note: Generic products are available for some formulations.	RPV (Edurant) <i>Tablet</i> <ul style="list-style-type: none"> 25 mg RPV/FTC/TDF (Complera) <ul style="list-style-type: none"> RPV 25-mg/ FTC 200-mg/ TDF 300-mg tablet RPV/DTG (Juluca) <ul style="list-style-type: none"> RPV 25-mg/ DTG 50-mg tablet RPV/FTC/TAF (Odefsey) <ul style="list-style-type: none"> RPV 25-mg/ FTC 200-mg/ TAF 25-mg tablet CAB and RPV (Cabenuva) <ul style="list-style-type: none"> CAB 200-mg/mL suspension for IM injection RPV 300-mg/mL suspension for IM injection 	Pregnancy <i>PK in Pregnancy</i> <ul style="list-style-type: none"> RPV PK 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. <i>Dosing in Pregnancy</i> <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. When standard dosing of RPV is received during pregnancy, viral loads should be monitored more frequently. <p>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., CAB, 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>DTG/RPV is not recommended for initial use in pregnancy because of the lack of available data about use in pregnancy. However, if DTG/RPV is well tolerated and associated with effective viral suppression when pregnancy occurs, this regimen can be continued with more frequent viral load monitoring (every 1–2 months) throughout pregnancy because the component drugs are recommended for use in pregnancy..</p> <p>Note: Please see FDA label for full list of drugs with potential interactions and drugs for which administration with RPV is contraindicated.</p>

Excerpt From Table 14

Generic Name (Abbreviation) <i>Trade Name</i>	Formulation	Dosing Recommendations^a	Use in Pregnancy
		Standard Adult Doses <i>RPV (Edurant)</i> <ul style="list-style-type: none"> • RPV 25 mg once daily with food <i>RPV/FTC/TDF (Complera)</i> <ul style="list-style-type: none"> • One tablet once daily with food <i>RPV/DTG (Juluca)</i> <ul style="list-style-type: none"> • One tablet once daily with food <i>RPV/FTC/TAF (Odefsey)</i> <ul style="list-style-type: none"> • One tablet once daily with food <i>CAB and RPV (Cabenuva)</i> <ul style="list-style-type: none"> • 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](#)).

^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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