Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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**Rilpivirine (Edurant, RPV)**

*(Last updated December 7, 2018; last reviewed December 7, 2018)*

The Antiretroviral Pregnancy Registry shows no difference between the overall risk of birth defects for rilpivirine and the background rate for major birth defects, which is 2.7% in the Metropolitan Atlanta Congenital Defects Program reference population.¹

**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 that resulted in drug exposure 3 times higher than seen in humans at the recommended dose of rilpivirine 25 mg once daily. Hepatocellular neoplasms were observed in both male and female mice at doses resulting in exposures 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/Adverse Pregnancy Outcomes**

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. Exposures were 15 and 70 times higher in pregnancy and lactation, respectively, than exposure in humans at the recommended dose of rilpivirine 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 study presenting pharmacokinetic (PK) and safety data from 32 pregnant women with HIV during pregnancy and postpartum found median rilpivirine 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 rilpivirine concentrations were significantly lower at 14 visits where the women had detectable HIV-1 RNA (30 ng/mL) than at 62 visits where they had 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.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 These authors recommended therapeutic drug monitoring in the third trimester, and attention to ensure that rilpivirine doses are taken with meals. A third study that compared rilpivirine exposure during pregnancy and postpartum noted approximately 30% decreases in total rilpivirine exposure and 22% to 25% decreases in unbound rilpivirine during pregnancy in 15 women.⁴ Cervicovaginal fluid rilpivirine concentrations were described in a study of 24 women taking rilpivirine daily during pregnancy and postpartum, which showed cervicovaginal rilpivirine steady-state concentrations similar to those seen in plasma in the same women. The rilpivirine cervicovaginal fluid to plasma AUC ratio was higher during pregnancy than postpartum.⁵ While rilpivirine plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied. Insufficient data are available to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored more frequently.

**Placental and Breast Milk Passage**

One of the PK and safety studies described above included rilpivirine delivery concentration data from 21 mother-infant pairs, with median (range) cord blood rilpivirine plasma concentration of 29.2 ng/mL (<10.0

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to 101.5 ng/mL), maternal delivery plasma rilpivirine concentration of 55.2 ng/mL (<10.0 to 233.8 ng/mL) and cord blood/maternal plasma ratio of 0.55 (0.3 to 0.8).2 Osiyemi et al. found that the median ratio of cord blood to maternal plasma concentration of total rilpivirine in 8 women was 0.55 (range: 0.43-0.98).4 Similarly, Schalkwijk et al. found a median (range) cord blood-to-maternal plasma ratio of 0.5 (0.35–0.81) in 5 women.4 An ex vivo human cotyledon perfusion model also showed that rilpivirine crosses the placenta with fetal transfer rates ranging from 17% to 37%.6,7 No data exist on whether rilpivirine is excreted in breast milk in humans.

Teratogenicity/Adverse Pregnancy Outcomes

Among cases of first-trimester exposures to rilpivirine reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 1.01% (3 of 297 births; 95% CI, 0.21% to 2.92%), whereas the total prevalence rate for the U.S. population is 2.7% based on Centers for Disease Control and Prevention surveillance.8

Excerpt from Table 10a

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

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine (RPV)</td>
<td>Edurant</td>
<td>Tablets:</td>
<td>Standard Adult Dose</td>
<td>Moderate to high placental transfer to fetus. b</td>
</tr>
<tr>
<td>(RPV/FTC/TDF)</td>
<td>Complera</td>
<td>• 25 mg RPV (Edurant)</td>
<td>RPV (Edurant):</td>
<td>No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</td>
</tr>
<tr>
<td>(RPV/DTG)</td>
<td>Juluca</td>
<td>RPV/FTC/TDF (Complera):</td>
<td>• 25 mg plus FTC 200 mg plus TDF 300 mg tablet</td>
<td>Two-drug regimens (e.g., RPV/DTG FDC) are not recommended in pregnancy.</td>
</tr>
<tr>
<td>(RPV/FTC/TAF)</td>
<td>Odefsey</td>
<td>RPV/DTG (Juluca):</td>
<td>• 25 mg plus DTG 50 mg tablet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPV/FTC/TAF (Odefsey):</td>
<td>• 25 mg plus FTC 200 mg plus TAF 25 mg tablet</td>
<td></td>
</tr>
</tbody>
</table>

Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

a 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; DTG = dolutegravir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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References


