Ritonavir (Norvir, RTV)

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Summary

- No dose adjustments are required for ritonavir (RTV) used as a booster during pregnancy.
- First-trimester exposure to RTV is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

RTV concentrations were lower during pregnancy than during the postpartum period when RTV was administered in combination with zidovudine and lamivudine to pregnant women with HIV at doses sufficient for HIV suppression in nonpregnant adults (500 mg or 600 mg twice daily).[1] RTV concentrations also are reduced during pregnancy compared with postpartum, when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors (PIs); however, RTV is an effective booster of the PIs lopinavir (LPV), atazanavir (ATV), and darunavir (DRV) in pregnant women.[2-4] By contrast, the newer booster, cobicistat, is not an effective booster of PIs in pregnant women, and its use is not recommended during pregnancy.[5]

Placental and Breast Milk Passage

In a human placental perfusion model, the clearance index of RTV was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.[6] In a Pediatric AIDS Clinical Trials Group trial 354 Phase 1 study of pregnant women and their infants, transplacental passage of RTV was minimal, with an average cord blood–to–maternal plasma concentration ratio of 5.3%.[1] In a study of cord blood samples from six women who were treated with RTV during pregnancy, the cord blood concentration was less than the assay limit of detection in five of the women and was only 0.38 mcg/mL in the remaining woman.[7] By contrast, in a study of hair and plasma RTV concentrations in 51 mother–infant pairs after lopinavir/ritonavir was administered to the mothers during pregnancy and postpartum, hair and plasma concentrations over time suggested moderate *in utero* transfer of LPV but negligible transfer via breastfeeding.[8]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to RTV to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of cardiovascular and genitourinary defects (the most common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with RTV. Among the cases of first-trimester RTV exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (88 of 3,554 live births; 95% confidence interval, 2.0% to 3.0%), compared with a total prevalence of 2.7% in the U.S. population, according to Centers for Disease Control and Prevention surveillance.[9]

Animal Studies

Carcinogenicity

RTV was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* screening tests. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at RTV doses of 50 mg/kg per day, 100 mg/kg per day, or 200 mg/kg per day; exposure (based on area under the curve) in male mice at the highest dose was approximately 0.3-fold the exposure observed in male humans who received the recommended therapeutic dose. No carcinogenic effects were observed in female mice at exposures that were 0.6-fold the exposures observed in women who received the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of the recommended therapeutic human exposure.[10]

Reproduction/Fertility

RTV has had no observed effect on reproductive performance or fertility in rats at drug exposures that were 40% (in males) and 60% (in females) of the exposures achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.[10]

Teratogenicity/Adverse Pregnancy Outcomes

No RTV-related teratogenicity has been observed in rats or rabbits. Developmental toxicity—including early resorptions, decreased body weight, ossification delays, and developmental variations (e.g., wavy ribs, enlarged fontanelles)—was observed in rats; however, these effects occurred only at maternally toxic dosages (with exposures equivalent to 30% of human therapeutic exposures). In addition, a slight increase in cryptorchidism was noted in rats at exposures equivalent to 22% of human therapeutic exposures. In rabbits, developmental toxicity (i.e., resorptions, decreased litter size, decreased fetal weight) also was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).[10]

Placental and Breast Milk Passage

Transplacental passage of RTV has been observed in rats with fetal tissue–to–maternal serum ratios >1.0 at 24 hours postdose in midgestational and late-gestational fetuses.

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
Ritonavir (RTV) *Norvir* (LPV/r) *Kaletra*	RTV (Norvir) *Capsule* • RTV 100 mg *Tablet* • RTV 100 mg *Oral Solution* • RTV 80 mg/mL *Powder* • RTV 100 mg/sachet LPV/r (Kaletra) *Tablets* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg *Oral Solution* • Each 5 mL contains LPV/r 400 mg/100 mg.	Pregnancy *PK in Pregnancy* • Lower RTV levels are seen during pregnancy than during postpartum, which may reduce the pharmaco-enhancing effect of RTV in pregnancy. *RTV Dosing in Pregnancy* • No dose adjustment is necessary when RTV is used as booster. *LPV/r Dosing in Pregnancy* • Once-daily dosing **is not recommended** during pregnancy. • Some experts recommend that an increased dose (i.e., LPV/r 600 mg/ 150 mg twice daily without regard to meals or LPV/r 500 mg/125 mg twice daily without regard to meals) should be used in the second and third trimesters of pregnancy, especially in patients who are PI-experienced and in those who start treatment during pregnancy with a baseline viral load >50 copies/mL. • When standard dosing is used, monitor virologic response and, if possible, LPV drug levels. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., LPV/r). Standard Adult Dose of RTV (Norvir) When Used as a PK Booster for Other PIs • RTV 100–400 mg per day in one or two divided doses (refer to other PI sections for specific dosing recommendations).	Low placental transfer to fetus[b] No evidence of increased risk of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) RTV should only be used as a low-dose booster for other PIs. RTV oral solution contains 43% alcohol and, therefore, **is not recommended** for use during pregnancy because no safe level of alcohol exposure during pregnancy is known. LPV/r oral solution contains 42% alcohol and 15% propylene glycol and **is not recommended** for use in pregnancy. Once-daily LPV/r dosing **is not recommended** during pregnancy.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		Tablet • Take with food. *Capsule or Oral Solution* • To improve tolerability, take with food, if possible. Standard Adult Doses of LPV/r (Kaletra) • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 mg once daily *Tablet* • Take without regard to food. *Oral Solution* • Take with food. With EFV or NVP in PI-Naive or PI-Experienced Patients • LPV/r 500-mg/125-mg tablets twice daily without regard to meals (use a combination of two LPV/r 200-mg/ 50-mg tablets and one LPV/r 100-mg/25-mg tablet), *or* • LPV/r 520-mg/130-mg oral solution (6.5 mL) twice daily with food	

[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; EFV = efavirenz; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetics; RTV = ritonavir

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