



**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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Ritonavir (Norvir, RTV)

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

Available data from the Antiretroviral Pregnancy Registry show no difference between the rate of overall birth defects in infants born to mothers who are taking ritonavir and the background rate of birth defects in a U.S. reference population. The Antiretroviral Pregnancy Registry has monitored a sufficient number of first-trimester exposures to be able to detect at least a 1.5-fold increase in risk of overall birth defects; however, no such increase has been observed. Use of ritonavir oral solution is not recommended during pregnancy, because this formulation contains alcohol and there is no known safe level of alcohol exposure during pregnancy.

Animal Studies

Carcinogenicity

Ritonavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at levels of ritonavir 50, 100, or 200 mg/kg/day; based on area under the curve, exposure in male mice at the highest dose was approximately 0.3-fold that seen in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of recommended therapeutic human exposure.¹

Reproduction/Fertility

No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.¹

Teratogenicity/Adverse Pregnancy Outcomes

No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles, was observed in rats; however, these effects occurred only at maternally toxic dosages (with exposures equivalent to 30% human therapeutic exposures). In addition, a slight increase in cryptorchidism was noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was also observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).¹

Placental and Breast Milk Passage

Transplacental passage of ritonavir has been observed in rats with fetal tissue-to-maternal-serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses.

Human Studies in Pregnancy

Pharmacokinetics

A Phase 1/2 safety and pharmacokinetic study (PACTG 354) of ritonavir (500 or 600 mg twice daily) administered in combination with zidovudine and lamivudine to pregnant women living with HIV showed lower levels of ritonavir during pregnancy than postpartum.² Ritonavir concentrations are also reduced during pregnancy versus postpartum when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors.^{3,4}

Placental and Breast Milk Passage

In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.⁵ In a Phase 1 study of pregnant women and their infants (PACTG 354), transplacental passage of ritonavir was minimal, with an average cord blood-to-

maternal-delivery concentration ratio of 5.3%.² In a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in five of the women and was only 0.38 micrograms/mL in the remaining woman.⁶ In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving lopinavir/ritonavir-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested *in utero* transfer of ritonavir: 2% of infants had detectable plasma ritonavir concentrations at birth, while mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.47 for ritonavir.⁷ However, transfer during breastfeeding was not observed, with no infant having detectable ritonavir plasma levels at 12 weeks.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with ritonavir. Among cases of first-trimester ritonavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (70 of 3,155 births; 95% CI, 1.7% to 2.8%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁸

Excerpt from Table 10^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Ritonavir (RTV) Norvir	<u>RTV (Norvir)</u> <i>Capsules:</i> • RTV 100 mg <i>Tablets:</i> • RTV 100 mg <i>Oral Solution:</i> • RTV 80 mg/mL <i>Powder:</i> • RTV 100 mg/sachet	<u>Standard Adult Dose as PK Booster for Other PIs:</u> • RTV 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations.) <i>Tablet:</i> • Take with food. <i>Capsule or Oral Solution:</i> • To improve tolerability, take with food if possible. <u>PK in Pregnancy:</u> • Lower levels seen during pregnancy than during postpartum. <u>Dosing in Pregnancy:</u> • No dosage adjustment necessary when used as booster.	Low placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Should only be used as low-dose booster for other PIs. Oral solution contains 43% alcohol and is therefore not recommended during pregnancy, because there is no known safe level of alcohol exposure during pregnancy.

^a 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](#)).

^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 to Acronyms: PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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