Lopinavir/Ritonavir (Kaletra, LPV/r)

Updated: March 31, 2026
Reviewed: March 31, 2026

Summary

- Lopinavir/ritonavir (LPV/r) concentrations are decreased by approximately 30% during pregnancy.
- Some experts recommend increased doses of LPV/r during the second and third trimesters of pregnancy (LPV/r 600 mg/150 mg twice daily or LPV/r 500 mg/125 mg twice daily), especially in protease inhibitor (PI)–experienced patients and patients who start treatment during pregnancy with a baseline viral load >50 copies/mL. Once-daily dosing of LPV/r during pregnancy **is not recommended.**
- First-trimester exposure to LPV/r is not associated with increased risk of congenital abnormalities.
- PI-based regimens, including LPV/r, may be associated with increased rates of preterm birth.
- LPV/r oral solution should not be used during pregnancy because it contains 42.4% alcohol and 15.3% propylene glycol.

Human Studies in Pregnancy

Pharmacokinetics

The original capsule formulation of LPV/r has been replaced by a heat-stable tablet formulation that has improved bioavailability characteristics and does not have to be administered with food.[1,2] Pharmacokinetic (PK) studies of standard adult LPV/r doses (400 mg/100 mg twice daily) that used either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir (LPV) plasma concentrations during pregnancy of around 30% compared with those seen in nonpregnant adults.[3-5] A further 33% reduction in LPV exposure was demonstrated in food-insecure, malnourished pregnant women in Uganda compared with historical well-nourished pregnant controls. The authors attributed this reduction to decreased bioavailability of LPV.[6] Increasing the dose of LPV/r during pregnancy to 600 mg/150 mg using the tablet formulation results in LPV plasma concentrations that are equivalent to those seen in nonpregnant adults who received standard doses.[7,8]

Clinical experience suggests that most, but not all, pregnant women who receive standard LPV/r tablet dosing during pregnancy will have LPV trough concentrations (C_{trough}) that exceed 1.0 mcg/mL, the usual target for C_{trough} in therapeutic drug monitoring programs for participants who are antiretroviral (ARV)-naive. However, higher C_{trough} are recommended for participants who are PI experienced, and some PI-experienced women who take the standard LPV/r dose during pregnancy will not achieve these concentrations.[1,4] A population PK study of LPV/r in 154 pregnant women demonstrated that body weight influences LPV clearance and volume of distribution; larger women (>100 kg) or women who missed a dose were at higher risk for subtherapeutic C_{trough} when taking the standard dose during pregnancy.[9] Another population PK study in 84 pregnant women and 595 nonpregnant adults found no significant difference between the LPV concentrations observed in pregnant women who were taking the more bioavailable tablet formulation and those seen in nonpregnant adults taking the original capsule formulation.[10] In one study of 29 women, LPV plasma protein binding was reduced during pregnancy, but the resulting increase in free (unbound) drug was insufficient to make up for the reduction in total plasma LPV concentration associated with

pregnancy.[11] In a study of 12 women, total LPV exposure was decreased significantly throughout pregnancy, but the area under the curve and concentration at 12 hours postdose for unbound LPV did not differ throughout pregnancy, even with an increased dose of LPV/r 500 mg/125 mg. Modeling of these data showed that standard dosing should be effective during pregnancy in people with susceptible virus.[12,13] A population PK study found a 39% increase in total LPV clearance during pregnancy, but measured unbound LPV concentrations in pregnancy were within the range of those simulated in nonpregnant adults.[14] Bonafe et al. randomized 32 pregnant women to receive the standard dose and 31 pregnant women to receive the 600 mg/150 mg dose of LPV/r at gestational ages between 14 and 33 weeks. No differences in adverse events were seen between groups. In women with baseline viral loads >50 copies/mL, 45% of women in the standard dose group had plasma viral loads >50 copies/mL during the last 4 weeks of pregnancy, compared with 10.5% of women in the increased dose group ($P = 0.01$). In women with baseline viral loads <50 copies/mL, no difference was seen between groups in viral load measurements during the last 4 weeks of pregnancy.[15]

These studies have led some experts to support the use of an increased dose of LPV/r during the second and third trimesters of pregnancy, especially in patients who are PI experienced and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. If possible, when standard doses of LPV/r are used during pregnancy, virologic response and LPV drug concentrations should be monitored. Instead of using three adult tablets (LPV/r 200 mg/50 mg each) to increase the dose of LPV/r to 600 mg/150 mg during pregnancy, clinicians may consider using two adult tablets and one pediatric LPV/r tablet (100 mg/25 mg) to provide a dose of LPV/r 500 mg/125 mg.[12] Once-daily dosing of LPV/r **is not recommended** in pregnancy because no data exist to address whether once-daily dosing produces adequate drug levels.

Placental and Breast Milk Passage

LPV crosses the human placenta; in the P1026s PK study (a Phase 4 PK study of selected ARV drugs used in pregnant women with HIV), the average ratio of LPV concentration in cord blood–to-LPV concentration in maternal plasma at birth was 0.20 ± 0.13. In contrast, in a study of 51 mother–infant pairs in Uganda in which the mother received LPV/r during pregnancy and breastfeeding, infant LPV plasma levels at birth and LPV hair levels at age 12 weeks suggested significant *in utero* transfer: 41% of infants had detectable plasma LPV concentrations at birth, and mean infant hair–to–maternal hair concentrations at 12 weeks postpartum were 0.87 for LPV.[16] However, transfer during breastfeeding was not observed, and no infant had detectable plasma LPV levels at 12 weeks. LPV concentrations in human breast milk are very low to undetectable, and LPV concentrations in breastfeeding infants whose mothers received LPV are not clinically significant.[16-21]

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort found no association between birth defects and LPV or ritonavir (RTV) use with 85% power to detect a 1.5-fold increase.[22] The Pediatric HIV/AIDS Cohort Study (PHACS) found no association between LPV and congenital anomalies.[23] Surveillance data from the United Kingdom and Ireland during a 10-year period showed that among the infants born after 4,609 LPV-exposed pregnancies, 134 infants had an identified birth defect, resulting in an overall congenital abnormality rate of 2.9%. This rate is comparable to rates of congenital abnormalities observed in populations without HIV.[24] The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for LPV/r 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 LPV/r to detect at least a 1.5-fold increase in risk of overall birth defects and at least a twofold increase in risk of birth defects in the cardiovascular and genitourinary systems (the more common classes of birth defects in the general population). No such increase in the risk of birth

defects has been observed with LPV/r. 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 LPV, RTV, 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) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 5.07 per 100 live births).

In the Promoting Maternal and Infant Survival Everywhere (PROMISE) study, administering LPV/r with zidovudine (ZDV) plus lamivudine (3TC) or with tenofovir disoproxil fumarate plus 3TC resulted in transmission rates that were lower than those seen with ZDV alone; however, the use of these LPV/r-containing regimens increased the incidence of low birth weight (<2,500 g).[25] Compared with ZDV alone, ZDV plus 3TC plus LPV/r was associated with increased rates of preterm birth (<37 weeks). The Surveillance Monitoring for Antiretroviral Therapy Toxicities (SMARTT) cohort of the PHACS also found an increased rate of preterm birth among women who received PI-based ARV therapy, although not with specific individual drugs.[26] Similarly, a study in China found that women who received PI-based regimens had higher rates of preterm birth than those who received non-nucleoside reverse transcriptase inhibitor (NNRTI)–based regimens.[27] In the United Kingdom/Ireland National Study of HIV in Pregnancy and Childhood, 2,368 out of 6,073 women had taken LPV/r during their pregnancies; after adjusting for other factors, the use of LPV/r carried a greater risk of preterm birth than the use of NNRTI-based regimens.[28] For a more detailed discussion of ARV drug regimens and adverse pregnancy outcomes, please refer to Antiretroviral Drug Regimens and Pregnancy Outcomes.

Other Safety Information

LPV/r oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol and **is not recommended** for use during pregnancy. Reduced hepatic metabolic function and kidney excretory function in newborns can lead to accumulation of LPV and of alcohol and propylene glycol, resulting in adverse events (e.g., serious cardiac, renal, metabolic, or respiratory problems). For more information about LPV/r use in newborns, refer to the Lopinavir/Ritonavir section in the Pediatric Antiretroviral Guidelines.[29,30]

Animal Studies

Carcinogenicity

Neither LPV nor RTV was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. Mice and rats showed an increased incidence of benign hepatocellular adenomas and an increased combined incidence of hepatocellular adenomas plus carcinoma at doses of approximately 1.6 times to 2.2 times (in mice) and 0.5 times (in rats) those seen in humans.[31]

Reproduction/Fertility

No effects on fertility were observed in male and female rats.[31]

Teratogenicity/Adverse Pregnancy Outcomes

In rats treated with a maternally toxic dose, embryonic and fetal developmental toxicities (i.e., early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations, and skeletal ossification delays) were observed. In a perinatal and postnatal study in rats,

a decrease in survival of pups between birth and postnatal Day 21 occurred. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dose. In pregnant mice, the use of RTV, LPV, and atazanavir was associated with significantly lower progesterone levels than those seen in mice who received no ARV drugs, and the lower progesterone levels correlated directly with lower fetal weight.[32]

Placental and Breast Milk Passage

No information is available on placental transfer of LPV in animals.[31]

Excerpt From Table 14

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Lopinavir/Ritonavir (LPV/r) *Kaletra* **Note:** Generic products are available for all formulations.	**LPV/r (Kaletra)**[c] *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* • With twice-daily dosing, LPV exposure is reduced in pregnant women who receive standard adult doses; increasing the dose by 50% results in exposure equivalent to that seen in nonpregnant adults receiving standard doses. • No PK data are available for once-daily dosing in pregnancy. *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, especially in PI-experienced pregnant women and women 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. **Standard Adult Doses** • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/20 mg once daily	Low placental transfer to fetus[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) 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. **Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with LPV/r is contraindicated.

Excerpt From Table 14

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
		Tablet • Take without regard to food. *Oral Solution* • Take with a meal. *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).

[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

[c] Generic formulation available

Key: ARV = antiretroviral; EFV = efavirenz; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic

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