

Lopinavir/Ritonavir (Kaletra, LPV/r)

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Animal Studies

Carcinogenicity

Neither lopinavir (LPV) nor ritonavir (RTV) was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The lopinavir/ritonavir (LPV/r) combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for ≤ 104 weeks. Results showed an increased incidence of benign hepatocellular adenomas and an increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and in male rats at doses that produced approximately 1.6 times to 2.2 times (in mice) and 0.5 times (in rats) the exposure seen in humans who received the recommended therapeutic dose of LPV/r 400 mg/100 mg (exposure was based on area under the curve [AUC]_{0–24hr} measurement). Administration of LPV/r did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.¹

Reproduction/Fertility

No effects on fertility were observed in male and female rats that received LPV and RTV at a 2:1 ratio. These rats experienced exposures that were approximately 0.7-fold (for LPV) and 1.8-fold (for RTV) the exposures seen in humans who received the recommended therapeutic dose.¹

Teratogenicity/Adverse Pregnancy Outcomes

No teratogenicity has been reported in studies where LPV/r was administered to pregnant rats and rabbits. In rats treated with a maternally toxic dosage (LPV/r 100 mg/kg and 50 mg/kg per day), 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. Drug exposure in the pregnant rats was 0.7-fold (for LPV) and 1.8-fold (for RTV) the exposures observed in humans who received the recommended therapeutic dose. In a perinatal and postnatal study in rats, a decrease in survival of pups between birth and postnatal day 21 occurred with exposure to LPV/r 40 mg/kg and 20 mg/kg per day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dose, when drug exposure was 0.6-fold (for LPV) and one-fold (for RTV) the exposures seen in humans who received the recommended therapeutic dose.¹ In a study of pregnant rats receiving chronic administration of zidovudine (ZDV), LPV, and RTV, maternal body weight gain was significantly reduced compared to weight gain in rats that received no antiretroviral (ARV) drugs, but no adverse effects were observed in fetuses.² 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 directly correlated with lower fetal weight.³

Placental and Breast Milk Passage

No information is available on placental transfer of LPV in animals.¹

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.^{4,5} Pharmacokinetic (PK) studies of standard adult LPV/r doses (400 mg/100 mg twice a day) that used either the capsule or tablet formulations in pregnant women have demonstrated a reduction in LPV plasma concentrations during pregnancy of around 30% compared with those seen in nonpregnant adults.^{6–8} A further 33% reduction in LPV exposure was demonstrated in food-insecure, malnourished pregnant women in Uganda compared to well-nourished, historical pregnant controls. The authors

attributed this reduction to decreased bioavailability of LPV.⁹ 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.^{10,11}

Clinical experience suggests that most, but not all, pregnant women who receive standard LPV/r tablet dosing during pregnancy will have trough LPV concentrations that exceed 1.0 mcg/mL, the usual target for trough concentration in therapeutic drug monitoring programs for ARV-naïve subjects. However, higher trough concentrations are recommended for protease inhibitor (PI)-experienced subjects, and some PI-experienced women who take the standard LPV/r dose during pregnancy will not achieve these concentrations.^{4,7} 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 trough concentrations when taking the standard dose during pregnancy.¹² 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.¹³ 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.¹⁴ In a study of 12 women, total LPV exposure was significantly decreased throughout pregnancy, but the AUC and concentration at 12 hours post dose (C_{12h}) 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.^{15,16} 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.¹⁷ 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 to 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.¹⁸

These studies have led some experts to support the use of an increased dose of LPV/r in pregnant women with HIV during the second and third trimesters, especially in women 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.¹⁵ 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 IV PK study of selected ARV drugs currently used in pregnant women with HIV), the average ratio of LPV concentration in cord blood to LPV concentration in maternal plasma at delivery 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 delivery 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-to-maternal-hair concentrations at 12 weeks postpartum were 0.87 for LPV.¹⁹ 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.¹⁹⁻²⁴

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort found no association between birth defects and LPV or RTV use with 85% power to detect a 1.5-fold increase.²⁵ The Pediatric HIV/AIDS Cohort Study found no association between LPV and congenital anomalies.²⁶ 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.²⁷ The Antiretroviral Pregnancy Registry 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. Among cases of first-trimester exposure to LPV/r reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.1% (30 infants out of 1,431 live births; 95% confidence interval, 1.4% to 3.0%) compared with a 2.7% total prevalence in the U.S. population based on the Centers for Disease Control and Prevention surveillance.²⁸

In the Promoting Maternal and Infant Survival Everywhere (PROMISE) study, administering LPV/r with 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).²⁹ Compared to ZDV alone, ZDV plus 3TC plus LPV/r was associated with increased rates of preterm delivery (<37 weeks). The Surveillance Monitoring for ART Toxicities (SMARTT) cohort of the Pediatric HIV/AIDS Cohort Study (PHACS) also found an increased rate of preterm birth among women who received PI-based ARV therapy, although not with specific individual drugs.³⁰ 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.³¹ 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 delivery than the use of NNRTI-based regimens.³² For a more detailed discussion of ARV drug regimens and adverse pregnancy outcomes, please refer to [Combination Antiretroviral Drug Regimens and Maternal and Neonatal 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 [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#).^{33,34}

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 10 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
Lopinavir/ Ritonavir (LPV/r) <i>Kaletra</i>	LPV/r (Kaletra) <i>Tablets:</i> <ul style="list-style-type: none"> LPV/r 200 mg/50 mg LPV/r 100 mg/25 mg <i>Oral Solution:</i> <ul style="list-style-type: none"> Each 5 mL contains LPV/r 400 mg/100 mg 	Standard Adult Doses <ul style="list-style-type: none"> LPV/r 400 mg/100 mg twice daily, <i>or</i> LPV/r 800 mg/200 mg once daily <i>Tablets:</i> <ul style="list-style-type: none"> Take without regard to food. <i>Oral Solution:</i> <ul style="list-style-type: none"> Take with meal. <i>With EFV or NVP in PI-Naive or PI-Experienced Patients:</i> <ul style="list-style-type: none"> 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), <i>or</i> LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food Pregnancy <i>PKs in Pregnancy:</i> <ul style="list-style-type: none"> 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. <i>Dosing in Pregnancy:</i> <ul style="list-style-type: none"> Once-daily dosing is not recommended during pregnancy. 	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.

		<ul style="list-style-type: none"> • 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. 	
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^aIndividual 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 10](#)).

^bPlacental 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: EFV = efavirenz; FDC = fixed-dose combination; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

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