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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Lopinavir/Ritonavir (Kaletra, LPV/r)

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No difference in the risk of overall major birth defects has been shown for lopinavir/ritonavir (LPV/r) compared to the background rate for major birth defects in the United States.

Animal Studies

Carcinogenicity

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The 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 increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and male rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of LPV/r 400 mg/100 mg (based on area under the curve $[AUC]_{0–24hr}$ measurement). Administration of LPV/r did not cause a statistically significant increase in 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 lopinavir in combination with ritonavir at a 2:1 ratio. These rats experienced exposures that were approximately 0.7-fold (lopinavir) and 1.8-fold (ritonavir) the exposures seen in humans at the recommended therapeutic dose.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence exists of teratogenicity with administration of LPV/r to pregnant rats or rabbits. In rats treated with a maternally toxic dosage (LPV/r 100 mg/50 mg/kg/day), embryonic and fetal developmental toxicities (e.g., 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 lopinavir and 1.8-fold for ritonavir the exposures observed in humans at 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/20 mg/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dose, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir the exposures seen in humans at the recommended therapeutic dose.[1] In a study of pregnant rats receiving chronic administration of zidovudine, lopinavir, and ritonavir, maternal body weight gain was significantly reduced compared to weight gain in rats that received no antiretroviral (ARV) drugs, but no adverse fetal parameters were observed.[2] In pregnant mice, ritonavir, lopinavir and atazanavir were 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 lopinavir in animals.[1]

Human Studies in Pregnancy

Pharmacokinetics

The original capsule formulation of LPV/r has been replaced by a tablet formulation that is heat-stable, 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) using either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir plasma concentrations during pregnancy of around 30% compared with those seen in nonpregnant adults.[6-8] Further reductions in lopinavir exposure by 33% were demonstrated in food-insecure, malnourished pregnant women in Uganda compared to well-nourished, historical pregnant controls. The authors attributed this reduction to decreased bioavailability.[9] Increasing the dose of LPV/r during pregnancy to 600 mg/150 mg (tablets) results in

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lopinavir plasma concentrations equivalent to those seen in nonpregnant adults receiving standard doses.[10,11]

Reports of clinical experience suggest that most, but not all, pregnant women receiving standard LPV/r tablet dosing during pregnancy will have trough lopinavir concentrations that exceed 1.0 mcg/mL, the usual trough concentration target used in therapeutic drug monitoring programs for ARV-naive subjects, but not the higher trough concentrations recommended for protease inhibitor (PI)-experienced subjects.[4,7] A population PK study of LPV/r in 154 pregnant women demonstrated that body weight influences lopinavir clearance and volume; 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 lopinavir concentrations observed in pregnant women taking the more bioavailable tablet formulation and those seen in nonpregnant adults taking the original capsule formulation.[13] In one study of 29 women, lopinavir 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 lopinavir concentration associated with pregnancy.[14] In a study of 12 women, total lopinavir exposure was significantly decreased throughout pregnancy, but unbound AUC and C_{12} did not differ throughout pregnancy, even with an increased dose of LPV/r 500 mg/125 mg. Modeling of these data concluded that standard dosing should be effective during pregnancy with susceptible virus.[15,16] A population PK study found a 39% increase in total lopinavir clearance during pregnancy, but measured unbound lopinavir 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 in 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 standard doses of LPV/r are used during pregnancy, virologic response and lopinavir drug concentrations should be monitored if possible. Instead of using three adult 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 drug levels are adequate with such administration.

Placental and Breast Milk Passage

Lopinavir crosses the human placenta; in the P1026s PK study, the average ratio of lopinavir concentration in cord blood to maternal plasma at delivery was 0.20 ± 0.13. In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda who received LPV/r during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested significant *in utero* transfer: 41% of infants had detectable plasma lopinavir concentrations at birth, and mean infant-to-maternal-hair concentrations at 12 weeks postpartum were 0.87 for lopinavir.[19] However, transfer during breastfeeding was not observed, and no infant had detectable plasma lopinavir levels at 12 weeks. Lopinavir concentrations in human breast milk are very low to undetectable, and lopinavir concentrations in breastfeeding infants whose mothers received lopinavir are not clinically significant.[19-23]

Teratogenicity/Adverse Pregnancy Outcomes

The French Perinatal Cohort found no association between birth defects and lopinavir or ritonavir with 85% power to detect a 1.5-fold increase.[24] The Pediatric HIV/AIDS Cohort Study found no association between lopinavir and congenital anomalies.[25] Surveillance data from the United Kingdom and Ireland over a 10-year period showed a 2.9% prevalence of congenital abnormalities (134 children out of 4,609 lopinavir-

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exposed pregnancies), comparable to rates of congenital abnormalities in populations without HIV.[26] In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to LPV/r have been monitored for detection of at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the cardiovascular and genitourinary systems. No such increase in 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 out of 1,418 births; 95% CI, 1.4% to 3.0%) compared with a prevalence of either 2.7% when using data from the Metropolitan Atlanta Congenital Defects Program (MACDP) or 4.2% when using data from the Texas Birth Defects Registry (TBDR).[27]

In the PROMISE study, LPV/r administered with zidovudine plus lamivudine or with tenofovir disoproxil fumarate plus lamivudine resulted in decreased transmission rates compared to the transmission rates seen with zidovudine alone, but these LPV/r-containing regimens also resulted in increased incidence of low birth weight (<2,500 g).[28] Compared to zidovudine alone, zidovudine plus lamivudine plus LPV/r was associated with increased rates of preterm delivery (<37 weeks). PHACS SMARTT also found an increased rate of preterm birth with PI-based ARV therapy, although not with specific individual drugs.[29] Similarly, a study in China found that PI-based regimens had higher rates of preterm birth than did non-nucleoside reverse transcriptase inhibitor-based regimens.[30] 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; LPV/r use was significantly associated with preterm delivery after adjustment for other factors when compared to other boosted-PI regimens or to NNRTI-based regimens.[31] 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.

Safety

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 and kidney excretory function in newborns can lead to accumulation of lopinavir as well as alcohol and propylene glycol, resulting in adverse events (e.g., serious cardiac, renal, metabolic, or respiratory problems).

Preterm babies may be at increased risk because their metabolism and elimination of lopinavir, propylene glycol, and alcohol are further reduced. Post-marketing surveillance has identified 10 neonates (i.e., babies aged <4 weeks), nine of whom were born prematurely, who received LPV/r and experienced life-threatening events.[32] In a separate report comparing 50 newborns exposed to HIV and treated with LPV/r after birth to 108 neonates exposed to HIV and treated with zidovudine alone, elevated concentrations of 17-hydoxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21α-hydroxylase activity, were seen only in the infants exposed to lopinavir. All full-term infants were asymptomatic, but three out of eight preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.[33] LPV/r oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth, plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained. Refer to Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for more information.

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Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name.*	Formulation	Dosing Recommendations	Use in Pregnancy
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	LPV/r (Kaletra) *Tablets (Coformulated):* • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg *Oral Solution:* • LPV/r 400 mg/100 mg/5 mL	Standard Adult Dose: • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 mg once daily *Tablets:* • Take without regard to food. *Oral Solution:* • Take with food. With EFV or NVP (PI-Naive or PI-Experienced Patients): • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of 2 LPV 200-mg plus RTV 50-mg tablets and 1 LPV 100-mg plus RTV 25-mg tablet), *or* • LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food PK in Pregnancy: • With twice-daily dosing, LPV exposure is reduced in pregnant women receiving 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. • If standard dosing is used, monitor virologic response and, if available, LPV drug levels.	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.

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

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