Lopinavir/Ritonavir (Kaletra, LPV/r)

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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 600/150 mg twice daily or LPV/r 500/125 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 delivery.
- 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The original capsule formulation of LPV/r has been replaced by a heat-stable tablet formulation that has improved bioavailability characteristics and does not have to be administered with food.[1,2] Pharmacokinetic (PK)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 antiretroviral (ARV)-naive subjects. However, higher C_{trough} are recommended for PI-experienced subjects, 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 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.[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 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 1,451 live births; 95% confidence interval, 1.4% to 2.9%) compared with a 2.7% total prevalence in the U.S. population based on Centers for Disease Control and Prevention surveillance.[25]

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).[26] Compared with 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 PHACS also found an increased rate of preterm birth among women who received PI-based ARV therapy, although not with specific individual drugs.[27] 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.[28] 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.[29] For a more detailed discussion of ARV drug regimens and adverse pregnancy outcomes, please refer to 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 the Lopinavir/Ritonavir section in the Pediatric Antiretroviral Guidelines.[30,31]

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.[32]

Reproduction/Fertility

No effects on fertility were observed in male and female rats.[32]

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.[33]

Placental and Breast Milk Passage

No information is available on placental transfer of LPV in animals.[32]

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 *PKs 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.

Excerpt from Table 14

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		Tablets • 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, 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

[c] Generic formulation available

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

References

1. Khuong-Josses MA, Azerad D, Boussairi A, Ekoukou D. Comparison of lopinavir level between the two formulations (soft-gel capsule and tablet) in HIV-infected pregnant women. *HIV Clin Trials*. 2007;8(4):254-255. Available at: https://pubmed.ncbi.nlm.nih.gov/17720666.

2. Else LJ, Douglas M, Dickinson L, et al. Improved oral bioavailability of lopinavir in melt-extruded tablet formulation reduces impact of third trimester on lopinavir plasma concentrations. *Antimicrob Agents Chemother*. 2012;56(2):816-824. Available at: https://pubmed.ncbi.nlm.nih.gov/22106215.

3. Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. *AIDS*. 2006;20(15):1931-1939. Available at: https://pubmed.ncbi.nlm.nih.gov/16988514.

4. Bouillon-Pichault M, Jullien V, Azria E, et al. Population analysis of the pregnancy-related modifications in lopinavir pharmacokinetics and their possible consequences for dose adjustment. *J Antimicrob Chemother*. 2009;63(6):1223-1232. Available at: https://pubmed.ncbi.nlm.nih.gov/19389715.

5. Ramautarsing RA, van der Lugt J, Gorowara M, et al. Thai HIV-1-infected women do not require a dose increase of lopinavir/ritonavir during the third trimester of pregnancy. *AIDS*. 2011;25(10):1299-1303. Available at: https://pubmed.ncbi.nlm.nih.gov/21516029.

6. Bartelink IH, Savic RM, Mwesigwa J, et al. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in Tororo, Uganda. *J Clin Pharmacol*. 2014;54(2):121-132. Available at: https://pubmed.ncbi.nlm.nih.gov/24038035.

7. Mirochnick M, Best BM, Stek AM, et al. Lopinavir exposure with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2008;49(5):485-491. Available at: https://pubmed.ncbi.nlm.nih.gov/18989231.

8. Best BM, Stek AM, Mirochnick M, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2010;54(4):381-388. Available at: https://pubmed.ncbi.nlm.nih.gov/20632458.

9. Cressey TR, Urien S, Capparelli EV, et al. Impact of body weight and missed doses on lopinavir concentrations with standard and increased lopinavir/ritonavir doses during late pregnancy. *J Antimicrob Chemother*. 2015;70(1):217-224. Available at: https://pubmed.ncbi.nlm.nih.gov/25261418.

10. Salem AH, Jones AK, Santini-Oliveira M, et al. No need for lopinavir dose adjustment during pregnancy: a population pharmacokinetic and exposure-response analysis in pregnant and nonpregnant HIV-infected subjects. *Antimicrob Agents Chemother*.

2016;60(1):400-408. Available at: https://pubmed.ncbi.nlm.nih.gov/26525798.

11. Aweeka FT, Stek A, Best BM, et al. Lopinavir protein binding in HIV-1-infected pregnant women. *HIV Med*. 2010;11(4):232-238. Available at: https://pubmed.ncbi.nlm.nih.gov/20002783.

12. Patterson KB, Dumond JB, Prince HA, et al. Protein binding of lopinavir and ritonavir during 4 phases of pregnancy: implications for treatment guidelines. *J Acquir Immune Defic Syndr*. 2013;63(1):51-58. Available at: https://pubmed.ncbi.nlm.nih.gov/23221983.

13. Chen J, Malone S, Prince HM, et al. Model-based analysis of unbound lopinavir pharmacokinetics in HIV-infected pregnant women supports standard dosing in the third trimester. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(3):147-157. Available at: https://pubmed.ncbi.nlm.nih.gov/27069778.

14. Fauchet F, Treluyer JM, Illamola SM, et al. Population approach to analyze the pharmacokinetics of free and total lopinavir in HIV-infected pregnant women and consequences for dose adjustment. *Antimicrob Agents Chemother*. 2015;59(9):5727-5735. Available at: https://pubmed.ncbi.nlm.nih.gov/26149996.

15. Bonafe SM, Costa DA, Vaz MJ, et al. A randomized controlled trial to assess safety, tolerability, and antepartum viral load with increased lopinavir/ritonavir dosage in pregnancy. *AIDS Patient Care STDS*. 2013;27(11):589-595. Available at: https://pubmed.ncbi.nlm.nih.gov/24138537.

16. Gandhi M, Mwesigwa J, Aweeka F, et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. *J Acquir Immune Defic Syndr*. 2013;63(5):578-584. Available at: https://pubmed.ncbi.nlm.nih.gov/24135775.

17. Rezk NL, White N, Bridges AS, et al. Studies on antiretroviral drug concentrations in breast milk: validation of a liquid chromatography-tandem mass spectrometric method for the determination of 7 anti-human immunodeficiency virus medications. *Ther Drug Monit*. 2008;30(5):611-619. Available at: https://pubmed.ncbi.nlm.nih.gov/18758393.

18. Shapiro RL, Rossi S, Ogwu A, et al. Therapeutic levels of lopinavir in late pregnancy and abacavir passage into breast milk in the Mma Bana Study, Botswana. *Antivir Ther*. 2013;18(4):585-590. Available at: https://pubmed.ncbi.nlm.nih.gov/23183881.

19. Palombi L, Pirillo MF, Andreotti M, et al. Antiretroviral prophylaxis for breastfeeding transmission in Malawi: drug concentrations, virological efficacy and safety. *Antivir Ther*. 2012;17(8):1511-1519. Available at: https://pubmed.ncbi.nlm.nih.gov/22910456.

20. Corbett AH, Kayira D, White NR, et al. Antiretroviral pharmacokinetics in mothers and breastfeeding infants from 6 to 24 weeks post-partum: results of the BAN Study. *Antivir Ther*. 2014;19(6):587-595. Available at: https://pubmed.ncbi.nlm.nih.gov/24464632.

21. Oumar AA, Bagayoko-Maiga K, Bahachimi A, et al. Efavirenz and Lopinavir Levels in HIV-Infected Women and Their Nursing Infants, in Mali. *J Pharmacol Exp Ther*. 2018;366(3):479-484. Available at: https://pubmed.ncbi.nlm.nih.gov/29986950.

22. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French Perinatal Cohort Study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: https://pubmed.ncbi.nlm.nih.gov/24781315.

23. Williams PL, Crain M, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):45-55. Available at: https://pubmed.ncbi.nlm.nih.gov/25383770.

24. Tookey PA, Thorne C, van Wyk J, Norton M. Maternal and foetal outcomes among 4118 women with HIV infection treated with lopinavir/ritonavir during pregnancy: analysis of population-based surveillance data from the national study of HIV in pregnancy and childhood in the United Kingdom and Ireland. *BMC Infect Dis*. 2016;16:65. Available at: https://pubmed.ncbi.nlm.nih.gov/26847625.

25. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2023. Morrisville, NC: Registry Coordinating Center; 2023.Available at: http://www.apregistry.com/. Accessed.

26. Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med*. 2016;375(18):1726-1737. Available at: https://pubmed.ncbi.nlm.nih.gov/27806243.

27. Van Dyke RB, Chadwick EG, Hazra R, et al. The PHACS SMARTT study: assessment of the safety of In utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://pubmed.ncbi.nlm.nih.gov/27242802.

28. Wang L, Zhao H, Tao J, et al. Risk factors associated with preterm and low birth weight among infants born to HIV-infected mothers in five tertiary hospitals in China, 2009-2014. Presented at: AIDS; 2016. Durban, South Africa.

29. Favarato G, Townsend CL, Bailey H, et al. Protease inhibitors and preterm delivery: another piece in the puzzle. *AIDS*. 2018;32(2):243-252. Available at: https://pubmed.ncbi.nlm.nih.gov/29135577.

30. Boxwell D, Cao K, Lewis L, et al. Neonatal toxicity of Kaletra oral solution: LPV, ethanol or prophylene glycol? Presented at: 18th Conference on Retroviruses and Opportunistic Infections; 2011. Boston, MA.

31. Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA*. 2011;306(1):70-78. Available at:

https://pubmed.ncbi.nlm.nih.gov/21730243.

32. Kaletra (Lopinavir and Ritonavir) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021251s059,021906s054lbl.pdf.

33. Papp E, Mohammadi H, Loutfy MR, et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. *J Infect Dis*. 2015;211(1):10-18. Available at: https://pubmed.ncbi.nlm.nih.gov/25030058.