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Randomized Clinical Trial Comparing the Pharmacokinetics of Standard- and Increased-Dosage Lopinavir-Ritonavir Coformulation Tablets in HIV-Positive Pregnant Women

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A lopinavir-ritonavir (LPV/r)-based regimen is recommended during pregnancy to reduce the risk of HIV mother-to-child transmission, but the appropriate dose is controversial. We compared the pharmacokinetics of standard and increased LPV/r doses during pregnancy. This randomized, open-label prospective study enrolled 60 pregnant women between gestational weeks 14 and 30. The participants received either the standard dose (400/100 mg twice a day [BID]) or increased dose (600/150 mg BID) of LPV/r tablets during pregnancy and the standard dose for 6 weeks after childbirth. Pharmacokinetics analysis was performed using a high-performance liquid chromatography-tandem mass spectrometry method. Adherent participants who received the standard dose presented minimum LPV concentrations of 4.4, 4.3, and 6.1 μg/ml in the second and third trimesters and postpartum, respectively. The increased-dose group exhibited values of 7.9, 6.9, and 9.2 μg/ml at the same three time points. Although LPV exposure was significantly higher in the increased-dose group, the standard dose produced therapeutic levels of LPV against wild-type virus in all adherent participants, except one patient in the third trimester; 50%, 37.5%, and 25%, and 0%, 15%, and 0% of the participants in the standard- and increased-dose groups failed to achieve therapeutic levels against resistant viruses during the second and third trimesters and after childbirth, respectively. After 12 weeks of treatment and after childbirth, all adherent participants achieved undetectable HIV viral loads, and their babies (49/54) were uninfected. No serious drug-related adverse events were observed. We conclude that the standard dose is appropriate for use during pregnancy and that an increased dose may be necessary for women harboring resistant HIV. (This study has been registered at ClinicalTrials.gov under registration no. NCT00605098.)

The number of women infected by the human immunodeficiency virus (HIV) worldwide has gradually increased in recent years (1). The majority of these women are of reproductive age, which increases the risk of HIV mother-to-child transmission (MTCT). The ability to reduce HIV MTCT rates through antiretroviral (ARV) use during pregnancy was first reported in 1994 (2); treatment efficacy is increased when combination ARV treatment (cART) is used from the second trimester of pregnancy on (3, 4).

Pharmacokinetics (PK) parameters may affect drug efficacy and toxicity (5). However, few studies have investigated the pharmacokinetics differences between women and men (6–8) and in pregnant women (9). Studies conducted with a small number of participants suggest that protease inhibitor (PI) levels in plasma are higher in women (10–12), although PI exposure decreases during pregnancy, especially in the third trimester (13).

The use of lopinavir coformulated with ritonavir (LPV/r) during pregnancy is recommended in the majority of HIV treatment guidelines (14–17), even though previous studies have been insufficient to determine the optimal LPV dose during pregnancy (18–24).

Well-designed ARV pharmacokinetics evaluations in HIV-infected pregnant women are required to ensure successful prevention of mother-to-child transmission (PMTCT) intervention strategies without compromising maternal health. The present study aimed to evaluate the pharmacokinetics of LPV and ritonavir (RTV) by comparing two different LPV/r doses (standard and increased) in pregnant women.

MATERIALS AND METHODS

Trial design and participants. This was a randomized, open-label prospective study (ClinicalTrials.gov registration no. NCT00605098) conducted at the Instituto de Pesquisa Clínica Evandro Chagas (IPEC), Fundação Oswaldo Cruz (Fiocruz), that enrolled 60 HIV-infected pregnant women between 14 and 30 gestational weeks from two clinical sites in the Rio de Janeiro metropolitan area, Brazil: the STD/AIDS Service of Hospital Geral de Nova Iguaçu (HGNI) and the Infectious Diseases Service of Hospital Federal dos Servidores do Estado do Rio de Janeiro (HFSE). Study participants were randomized in a 1:1 ratio using the SAS software (version 9.1.4) to receive either the standard dose (400/100 mg twice a day [BID]) or increased dose (600/150 mg BID) of lopinavir-ritonavir (LPV/r) tablets (Kaletra; Abbott Laboratories, Abbott Park, IL,

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USA) during the pregnancy. All participants continued to receive the standard dose of LPV/r for at least 6 weeks postpartum. The study was funded by the Brazilian Ministry of Health.

Study participants were eligible for inclusion if they met the following criteria: pregnant women aged ≥18 years, gestational age of 14 to 30 weeks, HIV infected and intended to continue combination antiretroviral (ARV) treatment (cART) for at least 6 weeks after delivery. The exclusion criteria included known hypersensitivity to LPV or RTV, use of concomitant medications with contraindications to the use of LPV/r, or any comorbidity that the physician deemed contraindicative to study participation.

Procedures. The institutional review board (IRB) of each participating institution approved this study; all participants signed informed consent (IC) prior to study enrollment.

HIV-1 viral load, T-lymphocyte subpopulations, complete blood count (CBC), chemistry, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lipids were evaluated at baseline and at quarterly visits.

Concomitant medication use was evaluated at each study visit. Adverse events (AEs) were recorded at each study visit and graded according to the Division of AIDS grading system (25). Treatment adherence was evaluated by patient self-reported adherence (3-day diary period) and through pill counts, calculated by the ratio of ARV pills returned at each visit to the number of pills dispensed in the previous visit.

Perinatal HIV-1 infection was documented by the detection of HIV RNA in plasma samples. Tests were performed between birth and 6 months, with a confirmatory test after 4 months if positive, and/or serologic test after 18 months of life.

Study dosing and pharmacokinetics sample collection. Pharmacokinetic evaluations were performed at least 2 weeks after treatment initiation at the following time points: second trimester (between 20 and 28 weeks of gestation), third trimester (between 30 and 36 weeks of gestation), at delivery, and postpartum (4 to 6 weeks after delivery), depending on the gestational age at study enrollment. Blood samples (8 ml) were drawn immediately before the morning LPV/r dose and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 h thereafter. Umbilical cord and maternal blood samples (10 ml) were drawn at birth to evaluate transplacental drug delivery. At each pharmacokinetics (PK) evaluation, the time of the last LPV/r dose was also recorded. Blood samples were centrifuged at 4,000 rpm for 10 min, and each plasma supernatant sample was aliquoted and stored at −70°C until assayed.

Analytic method. The LPV and RTV levels in plasma were determined by the Pharmacometry Laboratory at the Universidade Federal do Rio de Janeiro (UFRJ) using a validated high-performance liquid chromatography-tandem mass spectrometry method (HPLC-MS/MS) as previously reported (26). The assay ranges of LPV and RTV were 10 to 1,000 ng/ml and 2 to 300 ng/ml, respectively.

Pharmacokinetics analysis. Phoenix WinNonlin software (version 6.2.1) was used to determine the area under the concentration-time curve from 0 to 12 h (the last measurable concentration at 12 h) (AUC_{0-12}), plasma drug concentration at 12 h (C_{12}), peak or maximum drug concentration (C_{max}), minimum drug concentration (C_{min}), predose concentration (C_{pd}), total apparent oral clearance (CL/F), time to C_{max} (T_{max}), and time to C_{min} (T_{min}) by noncompartmental analysis. The ratio of the LPV levels in the umbilical cord and maternal blood were calculated as the ratio of the average values determined at delivery using the R software (version 2.14).

The primary endpoints were the LPV and RTV pharmacokinetics parameters AUC_{0-12}, C_{min}, C_{12}, C_{max}, C_{pd}, CL/F, T_{max}, and T_{min}. The maternal viral loads were measured 4 weeks after study treatment initiation and after delivery; AEs and perinatal transmission rates were defined as secondary endpoints.

Statistical analysis. Statistical analysis for the primary endpoints was performed only for the cART-adherent population at each PK evaluation moment. A cART adherence participant was defined according to the following criteria: >80% adherence according to pill counts, adherence of 100% according to patient self-reports and LPV C_{pd} of >0.2 μg/ml, the plasma LPV level used as a marker of nonadherence in previous therapeutic drug monitoring studies (12). Efficacy and safety endpoints were recorded for all participants who participated in at least one pharmacokinetics evaluation visit.

The χ^2 test was used for categorical data analysis. Numerical data were described using the mean and standard deviation and compared using the Wilcoxon and Kruskal-Wallis tests. Significant differences between groups were evaluated using the Tukey test ($P < 0.05$) using R software (version 2.14). Graphics were created using Origin (version 8.0) software.

A sample size of 20 participants/arm was determined to be sufficient to detect a difference of 30% in LPV AUC_{0-12} between the two arms with 80% power and an α of 0.05. A dropout rate of 25 to 30% was assumed. Thus, 30 subjects were included in each study arm.

RESULTS

Participants. Of the 72 pregnant women screened, 60 were enrolled and randomized (30 in each study arm) between January and September 2010. Of these 60 participants, 53 participated in at least one pharmacokinetics evaluation visit (Fig. 1).

Baseline demographic and clinical data from the 53 study participants are depicted in Table 1. Considering the baseline parameters, there were not statistically significant differences between the two groups. The mean age at baseline was 27 years, and the mean gestational age at enrollment was approximately 20 weeks. The mean $CD4^+$ T-cell count was 536 cells/mm^3. Forty-seven HIV-positive women were off treatment at the enrollment, 38 (72%) were naive, and 9 had received prophylaxis prior to study entry (5 in the standard-dose arm and 4 in the increased-dose arm), including 3 protease inhibitor (PI)-based regimens (1 nelfinavir and 2 LPV/r) and 6 nevirapine-based regimens. Six women received cART prior to pregnancy. Only one participant presented previous AIDS-defining illness (neurotoxoplasmosis). All study participants received coformulated zidovudine (ZDV) and lamivudine (3TC) (300/150 mg BID) in addition to LPV/r. Tenofovir (300 mg/day) was prescribed to one participant. All but one woman received ZDV intravenously (i.v.) during delivery, and 53/54 infants (98%) received ZDV orally (p.o.) for 6 weeks.

Pharmacokinetics analysis. Clinical data (treatment adherence, weight, gestational age, and time between the last dose and the first sample drawn for pharmacokinetics evaluation) and the pharmacokinetics parameters of LPV and RTV during the second and the third trimesters of pregnancy and postpartum are shown in Tables 2 and 3, respectively.

Although a high level of adherence was observed in both groups, a slightly lower adherence rate during pregnancy was observed in the LPV/r increased-dose arm.

The mean plasma LPV and RTV concentrations among pregnant women who received the standard and increased doses of LPV/r are shown in Fig. 2 and 3, respectively. Figure 4 compares the mean plasma LPV concentration profiles determined for the both arms during the third trimester. Participants who received the increased dose of LPV/r exhibited higher exposure to both drugs during pregnancy compared with those receiving the standard dose, even after postpartum dose reduction. The LPV and RTV curve concentration showed an absorption lag time mainly in the third trimester, most likely due to slower gastric emptying.

The LPV AUC_{0-12}, C_{min}, C_{pd}, C_{max}, and C_{12} were significantly different in the two arms (Table 3). At the second-trimester and postpartum assessments, all participants in both arms who were

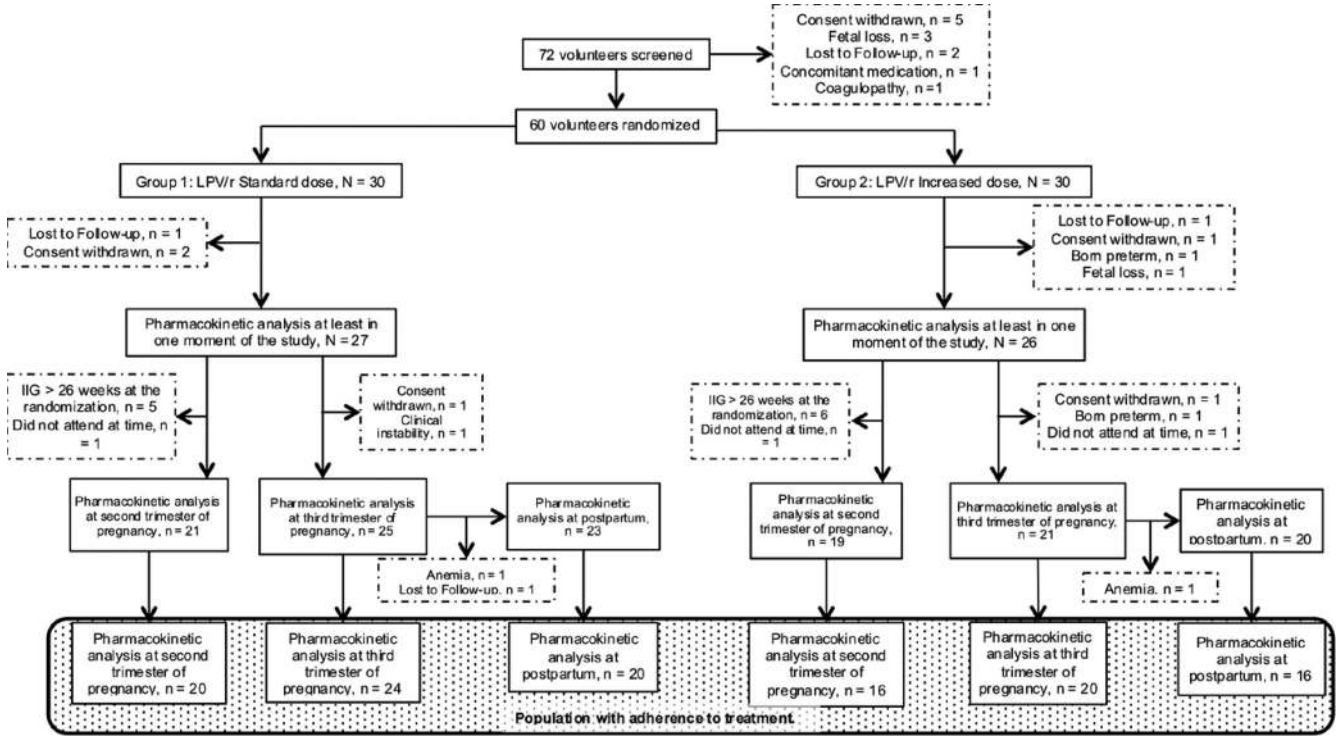

FIG 1 Patient flowchart.

considered adherent to cART (Fig. 1) presented a C_{min} of >1 μg/ml, which is the recommended efficacy threshold to block virus replication. At the third-trimester assessments, one participant in each arm exhibited a C_{min} of <1 μg/ml. At the second-trimester and postpartum assessments, all participants receiving the increased dose of LPV/r exhibited C_{min}s of >4 μg/ml, which is the therapeutic level considered effective for resistant viruses (12, 27). Conversely, in the LPV/r standard-dose group, 10/20 (50%) and 5/20 (25%) participants presented C_{min}s of <4 μg/ml at the second-trimester and postpartum assessments, respectively. During the third trimester, 37.5% (9/24) and 15% (3/20) of participants in the LPV/r standard- and increased-dose arms, respectively, exhibited C_{min}s below this target.

During the study, one participant in the standard-dose arm (at the third-trimester time point only) had a C_{min} of 0.9 μg/ml and AUC_{0-12} of <52 h · μg/ml, which is within the 10th percentile of AUC_{0-12} based on data from nonpregnant adults. This participant was adherent to cART but presented a CL/F of 11.7 liters/h, which is superior to the mean value observed for the standard-dose group at the third trimester (4.9 liters/h).

The LPV mean pharmacokinetics parameters C_{max}, AUC_{0-12}, T_{min}, C_{12}, and CL/F during pregnancy were significantly different than those at the postpartum visit ($P < 0.01$), particularly for the LPV/r standard-dose group, indicating that the increased LPV/r dose is associated with a greater similarity in the pharmacokinetics parameters during pregnancy and postpartum (Table 3). This difference was sustained even 4 weeks after delivery, when participants in both arms received the LPV/r standard dose.

The minimum RTV concentrations for adherent participants were 90.2, 106.4, and 190.2 ng/ml for the standard-dose arm and 205.8, 182.5, and 241.3 ng/ml for the increased-dose arm in the second trimester, third trimester, and postpartum, respectively.

TABLE 1 Demographic and clinical data for all study participants who participated in at least one pharmacokinetic evaluation visit ($n = 53$)

Characteristic[a]	Mean value (SD) or parameter value for participants		
	LPV/r standard dosing ($n = 27$)	LPV/r increased dosing ($n = 26$)	Total ($n = 53$)
Age (yr)	27.7 (5.7)	26.6 (5.7)	27.2 (5.7)
Gestational age (wk)	19.5 (5.6)	20.5 (5.7)	20.0 (5.7)
Wt, kg [median (IQR)]	61.7 (56.1–68.9)	58.9 (56.3–71.5)	60.1 (56.1–70.3)
ARV naive [no. (%)]	20 (74)	18 (69)	38 (72)
Nadir $CD4^+$ T cells (no. of cells/mm^3)	509 (174)	493 (155)	498 (165)
$CD4^+$ T cells (no. of cells/mm^3)	521 (156)	553 (151)	537 (154)
HIV viral load (log_{10})	3.5 (3.5)	3.6 (3.6)	3.6 (3.6)
Total time under study treatment (wk)	21.7 (6.5)	26.6 (5.7)	20.9 (6.8)

[a] IQR, interquartile range.

TABLE 2 Clinical data for all patients who participated in at least one pharmacokinetic evaluation visit ($n = 53$)[a]

Characteristic	Mean value or parameter value for participants					
	2nd trimester of pregnancy		3th trimester of pregnancy		Postpartum	
	LPV/r standard dose	LPV/r increased dose	LPV/r standard dose	LPV/r increased dose	LPV/r standard dose	LPV/r increased dose
Adherence to treatment [no. of participants who adhered to treatment/total no. of participants (%)]	20/21 (96)	16/19 (92)	24/25 (97)	20/21 (95)	20/21 (92)	16/20 (90)
Gestational age (wk) or time (wk after delivery)	21.7	22.2	31.1	31.2	5.2	4.7
Wt (kg)	65.7	66.8	68.2	67.9	66.4	64.6
Time (h) between the last dose and sample drawn	11.4	11.3	11.0	11.2	11.9	10.9

[a] Adherence to treatment, weight, gestational age, and time between the last dose and the first sample drawn for pharmacokinetic evaluation during the second and third trimesters of pregnancy and postpartum for all patients who participated in at least one pharmacokinetic evaluation visit.

The RTV AUC_{0-12}, C_{min}, C_{pd}, C_{max}, and C_{12} during pregnancy were significantly lower than those at the postpartum visit ($P < 0.04$), especially for the standard-dose LPV/r group.

Transplacental LPV and RTV levels. When 12 participants from the standard-dose arm and 7 participants from the increased-dose arm were evaluated, the mean LPV maternal plasma levels at delivery were 3.5 μg/ml and 4.0 μg/ml (with samples drawn 8.6 and 7.6 h after the last LPV/r dose), respectively. From the standard-dose arm and the increased-dose arm, the mean cord blood LPV levels were 0.7 and 1.0 μg/ml, and the mean cord blood/maternal plasma ratios were 0.20 and 0.18, respectively. At delivery, the mean RTV concentrations were 192.8 and 147.5 ng/ml in the maternal blood and 16.8 and 35.8 ng/ml in the cord blood for the standard- and increased-dose arms, respectively. No significant difference in LPV and RTV transplacental passage was detected between the two arms ($P = 0.67$ and $P = 0.81$, respectively).

Virologic response. After 4 weeks in the study, the participants in both arms had a progressively higher $CD4^+$ T-cell count and almost 80% of mothers had an undetectable viral load, including in those subjects deemed nonadherent. Only 9 participants presented a detectable HIV RNA viral load after 4 weeks of treatment, 4 were considered nonadherent, and 5 had low HIV RNA copy levels (between 72 and 96 copies/ml). After the 12th week of treatment and at the postpartum visit, all adherent participants had an undetectable viral load.

Treatment safety. Forty participants reported 80 clinical AEs during the study; 22 participants from the standard-dose arm reported 39 events, and 18 women from the increased-dose arm reported 41 events (Table 4). Grade 1 and 2 gastrointestinal events, including cramps, and headache related to LPV were reported. The only laboratory AE related to the use of the study medication was dyslipidemia, and this was more frequent in the LPV/r increased-dose arm (Table 5). Overall, the low frequency of AEs did not permit the detection of significant differences between the study arms. No AE led to participant study discontinuation in either treatment group.

Pregnancy endpoints. A total of 53 participants were included in the safety analysis, and 54 infants were delivered: 28 from the standard-dose arm mothers and 26 from the increased-dose arm mothers. There were four premature deliveries (7.6%), two in each arm. Nineteen (35.9%) pregnant women had vaginal deliveries (6 from the standard-dose arm and 13 from the increased-dose arm), 7 women (13.2%) had emergency caesarean deliveries (4 from the standard-dose arm and 3 from the increased-dose arm), and 27 women (50.9%) had elective caesarean deliveries (15

TABLE 3 Pharmacokinetic parameters of lopinavir and ritonavir during the second and third trimesters of pregnancy and postpartum for the cART-adherent population at each PK evaluation moment

Drug and pharmacokinetic parameter	Pharmacokinetic parameter[a] in the 2nd trimester of pregnancy			Pharmacokinetic parameter in the 3th trimester of pregnancy			Pharmacokinetic parameter postpartum		
	LPV/r standard dose ($n = 20$)	LPV/r increased dose ($n = 16$)	*P* value (Wilcoxon)[b]	LPV/r standard dose ($n = 24$)	LPV/r increased dose ($n = 20$)	*P* value (Wilcoxon)	LPV/r standard dose ($n = 20$)	LPV/r increased dose ($n = 16$)	*P* value (Wilcoxon)
Lopinavir									
T_{max}, h [median (IQR)]	3.0 (3.0–4.8)	3.5 (3.0–5.0)	0.61	4.0 (3.0–5.0)	4.0 (4.0–5.0)	0.35	4.0 (3.0–5.8)	4.0 (3.3–5.0)	0.99
C_{max} (μg/ml)	10.8 (2.6)	16.3 (4.0)	**<0.001**	10.9 (2.5)	15.9 (5.0)	**<0.001**	14.4 (3.7)	17.2 (4. 5)	0.05
AUC_{0-12} (h · μg/ml)	88.4 (25.6)	139.4 (34.8)	**<0.001**	87.2 (21.1)	130.7 (38.8)	**<0.001**	122.4 (29.9)	154.0 (44.8)	0.04
T_{min}, h [median (IQR)]	12.0 (8.0–12.0)	12.0 (4.3–12.0)	0.89	12.0 (12.0–12.0)	12.0 (10.0–12.0)	0.61	1 (0–11.5)	12.0 (0–12.0)	0.21
C_{min} (μg/ml)	4.5 (1.9)	8.0 (2.6)	**<0.001**	4.3 (1.6)	7.0 (3.0)	**<0.001**	6.1 (2.3)	9.2 (3.7)	**0.005**
Clearance (liter/h)	4.9 (1.3)	4.6 (1.2)	0.47	4.9 (1.7)	5.0 (1.7)	0.8	3.5 (0.9)	4.2 (1.2)	0.06
Ritonavir									
T_{max}, h [median (IQR)]	4.0 (4.0–4.8)	4.0 (4.0–5.0)	0.81	4.0 (4.0–5.0)	4.0 (4.0–5.0)	0.81	4.0 (3.0–5.0)	4.0 (3.3–5.0)	0.73
C_{max} (ng/ml)	873.4 (400.7)	1,704.8 (760.2)	**0.001**	842.6 (383.1)	1,762.0 (1,095.1)	**<0.001**	1419.0 (519.8)	1737.3 (1108.2)	0.85
AUC_{0-12} (h · ng/ml)	4,127.9 (1,541.3)	8,495.7 (3,619.6)	**<0.001**	4,326.9 (1,359.9)	7,810.2 (4,145.5)	**0.002**	7,264.0 (2,545.4)	9,441.1 (5,274.4)	0.40
T_{min}, h [median (IQR)]	12.0 (12.0–12.0)	12.0 (12.0–12.0)	0.48	12.0 (12.0–12.0)	12.0 (12.0–12.0)	0.86	10.0 (1.0–12.0)	12.0 (12.0–12.0)	**0.02**
C_{min} (ng/ml)	90.2 (47.5)	205.8 (139.6)	**0.003**	106.4 (45.4)	182.5 (118.4)	**0.05**	190.2 (101.2)	241.3 (101.3)	0.15
Clearance (liter/h)	29.0 (15.5)	21.8 (12.0)	**0.05**	27.4 (17.2)	25.4 (14.3)	0.65	15.7 (6.3)	20.2 (9.1)	0.12

[a] Values are means (standard deviations) unless specified otherwise.

[b] *P* values that are significantly different for the values for the two arms are shown in boldface type.

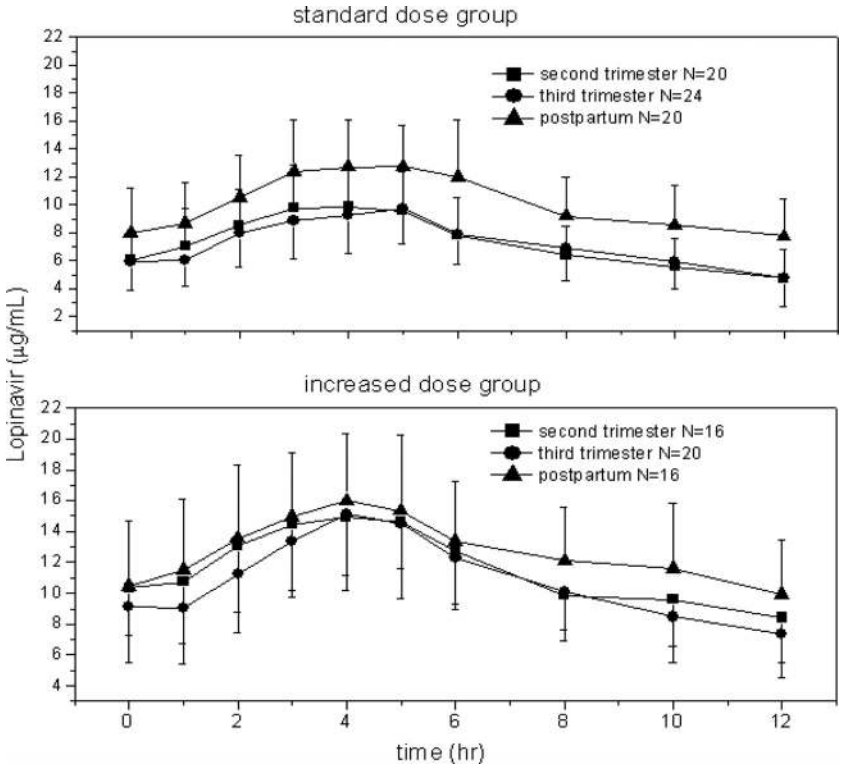

FIG 2 Mean plasma LPV concentration according to LPV/r dose, evaluation time point (second and third trimester of pregnancy and postdelivery) for the cART-adherent population at each PK evaluation moment. Values are means ± standard deviations (SD) (error bars).

from the standard-dose arm and 12 from the increased-dose arm). The infants' mean weight at delivery was 2.98 kg in both arms. Low birth weight (<2.5 kg) was observed in 14.3% (4/28 participants of the standard-dose arm) and 11.5% (3/26 participants of the increased-dose arm) of infants, all considered premature. Congenital abnormalities were observed in five infants: two cases of hemangioma (one in each arm) and three cases of inguinal hernias (one from the standard-dose arm and two from the increased-dose arm).

Infant HIV serologic status. Among the 54 neonates, 5 infants (9.3%) were not evaluated for HIV status: 3 neonates died before the final diagnosis (1 premature infant from the standard-dose arm and 2 neonates from the increased-dose arm). The causes of death were neonatal sepsis at 19 days of life, gastroenteritis at 2 months of life, and aspiration pneumonia at 3 months of life, respectively. The consent was withdrawn before the end of the study for two neonates (one from each arm). All of the remaining 49 infants evaluated were uninfected.

DISCUSSION

In the present study, we compare the pharmacokinetics profiles of LPV/r administered in two dosage regimens, namely, the standard dose (2 tablets BID) and increased dose (3 tablets BID), which is recommended for HIV-infected pregnant women by several treatment guidelines and studies. Participants in the increased-dose arm showed increased LPV/r exposure and a greater similarity in pharmacokinetics parameters during pregnancy and after delivery. LPV AUC values for patients in the increased-dose arm were higher than the AUC values reported for nonpregnant adults (28) but were consistent with pharmacokinetics parameters determined for non-Caucasian adults with low body weight (29). Even producing lower LPV exposure during pregnancy, LPV standard dose was sufficient to provide LPV AUC similar to 82.8 h · μg/ml, the 50th percentile AUC of LPV in nonpregnant adults (28). After delivery, LPV AUC of the standard-dose arm increased to 122.4 h · μg/ml, which was also observed in the increased-dose arm (154.0 h · μg/ml). Considering both study arms, LPV exposure was similar only for the postpartum period, when AUC and C_{max} did not differ significantly.

The lower LPV/r exposure during pregnancy demonstrated by our and other previous studies (19, 24, 30) was probably related to bioavailability and CL/F alterations in this period. In our study, CL/F was higher during pregnancy, compared to postpartum, especially in the standard-dose arm ($P < 0.001$). In an evaluation of 33 pregnant women receiving LPV/r tablets, LPV CL/F values were 5.6, 6.2, and 3 liters/h in the second and third trimesters and postpartum, respectively (19). In another study of pregnant women receiving LPV soft-gel capsules, the mean CL/F value was 9 liters/h antepartum and decreased to 6.1 liters/h postpartum (29).

All adherent participants had AUC and C_{min} above the target values, with the exception of one participant. An LPV C_{min} below 1 μg/ml (minimum effective concentration in treatment-naive HIV adult participants) was related to poor adherence to treatment, as evaluated by pill count and participant self-reported adherence. These observations reaffirm that adherence to treatment is one of the most important factors in successful HIV therapy (12, 23, 31), including during pregnancy (9, 32).

Participants receiving the standard LPV/r dose and considered

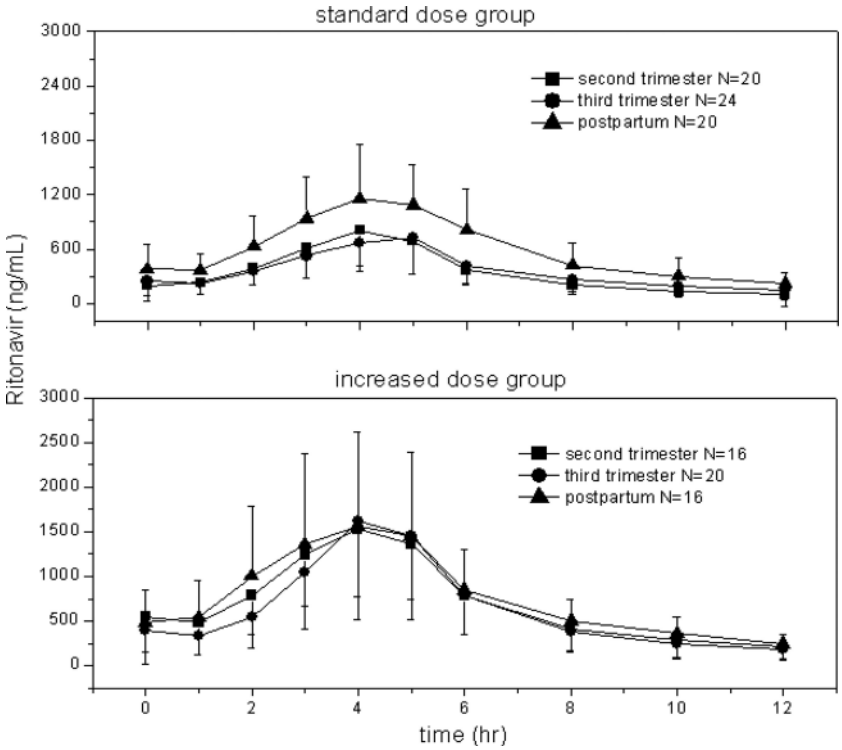

FIG 3 Mean plasma RTV concentration according to LPV/r dose, evaluation time point (second and third trimester of pregnancy and postdelivery) for the cART-adherent population at each PK evaluation moment. Values are means plus or minus SD (error bars).

adherent to the treatment exhibited mean LPV C_{min} similar to those observed for pregnant women in Thailand (22), United States (33), and United Kingdom (24) (Table 6). The weights of the participants from these studies were similar to the weights of the participants of our study.

The C_{min} and C_{pd} values of the LPV/r standard-dose arm were also similar to those reported in two therapeutic drug monitoring (TDM) trials conducted with pregnant women using this LPV/r dose (18, 21) (Table 6). However, the average body weight of those participants was higher than the mean weights of our participants and those from the previously cited studies. One of the limitations of TDM studies is that only predose levels are determined, and thus, concentrations can be overestimated if there is an absorption lag time, as was demonstrated in our LPV and RTV plasma profiles, most notably in the third trimester of pregnancy.

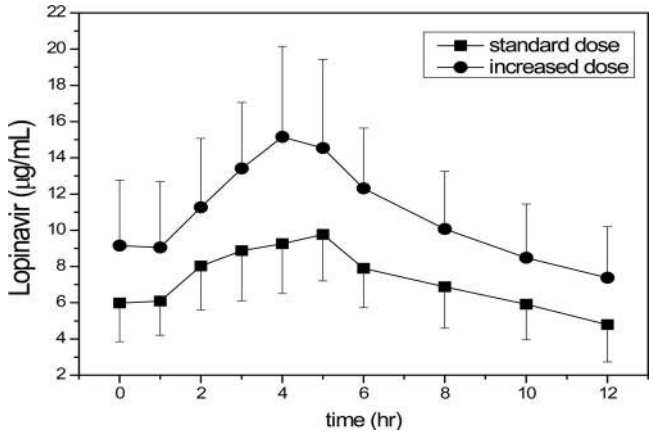

FIG 4 Mean plasma LPV concentration to standard and increased doses of LPV/r during the third trimester of pregnancy for the cART-adherent population. Values are means plus or minus SD (error bars).

In six studies using LPV tablets (400 mg/100 mg) in pregnant women, the standard dose of LPV/r was sufficient to maintain HIV suppression, and an increase in the daily number of tablets was not recommended (18, 20–22, 24, 33). Patterson and colleagues (33) performed two pharmacokinetics analyses with the same patient population in the third trimester of pregnancy, who first received a standard dose of LPV/r before transitioning to an increased LPV/r dose after 2 weeks. Similar minimum concentration values were observed for the standard and increased dose (4.0 and 4.9 μg/ml, respectively), and both were above the target for therapy against resistant virus (4.0 μg/ml). Although the increased dose was associated with an increase in AUC values (89.1 h · μg/ml versus 54.1 h · μg/ml), the standard dose was sufficient to achieve the target of 52 h · μg/ml, which is the 10th percentile AUC_{0-12} of LPV for nonpregnant adults.

Best and colleagues (19) conducted a study of pregnant women using the standard dose of LPV/r during the second trimester and postpartum and increased dose (6 pills a day) during the third trimester, based on previous results that demonstrated a reduction of the C_{min} and AUC values in the third trimester of pregnancy when LPV/r was administered in soft-gelatin capsules (29). The minimum concentration values determined in the second trimester and postpartum were 3.4 and 6.9 μg/ml, with AUC values of 72 and 133 h · μg/ml, respectively, and 2/11 (18.2%) and 2/27 (7.4%) of the participants presented a C_{min} of <1 μg/ml. Participants receiving an LPV/r increased dose at the third trimes-

TABLE 4 Clinical adverse events occurring in all patients who participated in at least one pharmacokinetic evaluation visit ($n = 53$)

Adverse event	LPV/r standard dosing ($n = 27$)		LPV/r increased dosing ($n = 26$)	
	Total no. of patients with adverse event (%)	No. of patients with adverse event related to LPV/r (%)	Total no. of patients with adverse event (%)	No. of patients with adverse event related to LPV/r (%)
Headache (grade 1)	2 (7.4)	0	4 (15.4)	1 (3.9)
Abdominal pain (grade 1 and grade 2)	1 (3.7) and 3 (11.1)	0 and 1 (3.7)	2 (7.7) and 2 (7.7)	0 and 2 (7.7)
Diarrhea (grade 1 and grade 2)	6 (22.2) and 1 (3.7)	6 (22.2) and 1 (3.7)	3 (11.5) and 1 (3.9)	3 (11.5) and 1 (3.9)
Nausea (grade 1 and grade 2)	1 (3.7) and 1 (3.7)	1 (3.7) and 1 (3.7)	6 (23.1) and 3 (11.5)	6 (23.1) and 3 (11.5)
Vomiting (grade 1)	6 (22.2)	6 (22.2)	3 (11.5)	3 (11.5)
Bronchitis (grade 2)	1 (3.7)	0	0	0
Vaginal candidiasis (grade 1)	1 (3.7)	0	2 (7.7)	0
Backache (grade 1)	1 (3.7)	0	2 (7.7)	0
Extremity edema (grade 2)	1 (3.7)	0	0	0
Scabies (grade 1)	1 (3.7)	0	1 (3.9)	0
Genital herpes (grade 1)	1 (3.7)	0	0	0
Wound infection (grade 3)	0	0	1 (3.9)	0
Urinary tract infection (grade 2)	2 (7.4)	0	3 (11.5)	0
Upper respiratory tract infection (grade 1)	4 (14.8)	0	2 (7.7)	0
Superficial mycoses (grade 1)	1 (3.7)	0	2 (7.7)	0
Myositis associated with pyelonephritis (grade 3)	1 (3.7)	0	0	0
Otitis (grade 1)	2 (7.4)	0	1 (3.9)	0
Worsening of hypertension (grade 5)	1 (3.7)	0	0	0
Vaginal bleeding-placenta previa (grade 2)	0	0	1 (3.9)	0
Sinusitis (grade 2)	1 (3.7)	0	2 (7.7)	0
Total	39	16	41	19

ter had a C_{min} of 4.9 μg/ml and AUC of 96 h · μg/ml, and only 2/33 (6.1%) of the participants did not achieve a C_{min} of 1 μg/ml (19). In our study, the adherent participants achieved C_{min} (7.0 μg/ml) and AUC_{0-12} (130.7 h · μg/ml) values higher than those reported by Best et al. (19). However, the mean weight reported in that study was almost 10 kg higher (77.8 kg) than the mean reported in this and other studies (18, 21, 33). The higher LPV exposure levels in our participants could be explained by the lower body weights of our participants; every 10 kg of additional corporal weight is related to a 11% decrease in plasma drug levels (34). Another difference between the present study and the studies mentioned above is in the ethnic composition of the study participants; 100% of the participants in the Thailand studies were Asian, and the participants in the United States and European studies were predominantly black, whereas 44.4% of the women in our study population identified themselves as white. Pharmacogenetic characteristics related to ethnicity can affect the pharmacokinetics of some drugs (35, 36), as has already been demonstrated in studies evaluating the pharmacokinetics and pharmacogenetics of LPV in adults and children from the United States (37, 38). Correlating pharmacogenetic studies with race and ethnicity can cause misinterpretation (39), especially in Brazil, where the genetic characteristics reflect miscegenation among Amerindians, Europeans, and Africans (40). Self-reported race, one parameter used in our study, can be a confounding factor because in Brazilian culture, self-identified race is more affected by socially constructed factors than by skin color (41). Nevertheless, genetic characteristics, as well as environmental factors, diet, smoking, or herbal intake and concomitant illness, cannot be discarded as a potential factor associated with the differences in the LPV pharmacokinetics between this study and the previously mentioned clinical trials (19, 20, 29, 42).

In addition, the high interindividual variability in PI plasma levels, which is approximately 34% for the LPV/r tablet formulation (43), suggests that the comparison of the C_{min} and LPV therapeutic levels is more reliable than a simple comparison of the mean values of the various pharmacokinetics parameters reported by different studies. In our study, interindividual variability was excluded by the comparison of results from the same participants during pregnancy and after delivery, which indicated that LPV exposure is truly lower in pregnant women at any period of pregnancy than in nonpregnant adults.

TABLE 5 Laboratorial adverse events occurring in all patients who participated in at least one pharmacokinetic evaluation visit ($n = 53$)

Adverse event and grade[a]	No. of patients with adverse event (%)	
	LPV/r standard dosing ($n = 27$)	LPV/r increased dosing ($n = 26$)
Anemia (grade 1)	4 (14.9)	3 (11.5)
Increased ALT/AST (grade 1)	1 (3.7)	0
Increased total cholesterol		
Grade 1	3 (11.1)	4 (15.4)
Grade 2	2 (7.4)	2 (7.7)
Increased LDL		
Grade 1	3 (11.1)	4 (15.4)
Grade 2	2 (7.4)	2 (7.7)
Increased triglycerides		
Grade 1	1 (3.7)	2 (7.7)
Grade 2	2 (7.4)	1 (3.9)
Any abnormal result in urinalysis	7 (25.9)	5 (19.2)

[a] ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein.

TABLE 6 Minimum and predose concentrations of LPV (400/100 mg BID) and comparison with published data

Reference	Wt (kg)	C_{min} (μg/ml)			C_{pd} (μg/ml)		
		2nd trimester	3rd trimester	Postpartum	2nd trimester	3rd trimester	Postpartum
This study	61.8–69.4[a]	4.5	4.3	6.1	6.1	6.0	8.0
Khuong-Josses et al. (18)						4.6	
Lambert et al. (21)	88 (49–103)[b]				3.5	3.3	5.1
Ramautarsing et al. (22)	54.9/60.1/56.3[c]	2.4	3.2	4.7			
Else et al. (24)	77 (55–116)[b]	4.6	2.5	4.7	5.7	3.7	6.1
Patterson et al. (33)		5.2	4.0	7.2			

[a] The range is shown.
[b] Values are given as median (range).
[c] Values at 2nd and 3rd trimester and postpartum.

Considering only the adherent participants, the C_{min} values were lower for the LPV/r standard-dose arm (4.5, 4.3, and 6.1 μg/ml in the second and third trimesters of pregnancy and postpartum, respectively) than for nonpregnant adults (5.5 μg/ml) (43), whereas the C_{min} values for the LPV/r increased-dose arm (8.0, 7.0, and 9.2 μg/ml, respectively) were higher. The same observation applies to the AUC values determined at all stages of pregnancy and the mean AUC value for nonpregnant adults (92.6 h · μg/ml). These results confirm our finding that LPV exposure during pregnancy in the standard-dose group was lower than that for nonpregnant adults or pregnant women using an increased dose. The standard dose, in pregnant women, was sufficient to yield therapeutic LPV levels against wild HIV type virus and to maintain an AUC within the target range.

Of note, 50%, 37.5%, and 25% of the cART-adherent participants in the standard-dose arm did not achieve LPV levels considered therapeutic for resistant viruses (4 μg/ml) in the second and third trimesters and postpartum, respectively. The only previous study that performed this type of analysis reported that 17.8% of the participants had LPV therapeutic levels for resistant viruses at the third trimester of pregnancy (18). In our study, all participants receiving an increased LPV/r dose presented a C_{min} of >4 μg/ml in the second trimester and postpartum, and 85% had a C_{min} of >4 at the third trimester of pregnancy. Even 4 weeks after delivery, at which point all participants were receiving the standard dose of LPV/r, the minimum concentration in the increased-dose group was higher (9.2 versus 6.1 μg/ml; $P = 0.005$), indicating that LPV dose could be reduced immediately after delivery without compromising the treatment efficacy. However, the clinical significance of these results is unknown; only a small number of participants that harbored resistant HIV was included in the pharmacokinetics study, and correlations of C_{min} and AUC with virologic response could not be performed.

Approximately 99% of LPV is highly bound to plasma protein. During pregnancy, unbound LPV increases, which compensates for the low level of plasma LPV observed in this period and also compensates for a portion of the decrease in the LPV plasma levels observed during pregnancy. Therefore, the fact that no cases of perinatal transmission were observed in this trial indicates that lower LPV exposure (especially in the third trimester) is not necessarily relevant to the efficacy of the prophylactic scheme. Furthermore, LPV/r dose adjustment during pregnancy can negatively impact adherence to cART, which is usually lower in treatments with a high pill burden (44). Nevertheless, for participants with suspected or confirmed PI-resistant virus, the higher exposure obtained with an increased dose of LPV/r is appropriate and recommended until additional data become available.

The comparison of the pharmacokinetics parameters of ritonavir in the two arms revealed significant differences during pregnancy and postpartum, following the same pattern as observed in LPV. The participants receiving an increased dose had similar exposure to RTV during pregnancy and postpartum, and the standard dose resulted in lower exposure during pregnancy than postpartum.

The minimum RTV concentrations in adherent participants were similar to those reported by previous studies (19, 20, 22, 24, 43). These results demonstrate that the RTV exposure of pregnant women receiving a standard dose of LPV/r is similar to that of nonpregnant adults and most likely not responsible for the decreased LPV exposure during pregnancy.

The efficacy of the standard dose of LPV/r in our study, as determined by the proportion of participants presenting an undetectable viral load after 12 weeks of treatment, was similar to the efficacy of the increased dose, as all adherent participants achieved HIV RNA values lower than 50 copies/ml within this period. Similarly, in other studies of LPV/r pharmacokinetics in pregnant women, an undetectable viral load in the third trimester was observed in 89% (24), 95% (22), 96% (23), and 100% (20) of participants receiving a standard dose and in 86% of participants receiving an increased LPV/r dose (19). In these studies, participants with a detectable viral load had HIV RNA values below 400 copies/ml, indicating that the use of an LPV/r standard dose during pregnancy is associated with a low risk of resistance mutation selection, despite the lower exposure to PI.

The efficacy of the LPV/r standard dose in preventing HIV MTCT was also evaluated. The data from our study were comparable to other reported results (21, 22, 24, 33); none of the babies evaluated (49/54) was infected.

The treatment safety evaluation indicated that standard and increased doses of LPV/r appeared well tolerated and safe, and no treatment discontinuation was necessary in either treatment group. The incidence of adverse events with LPV/r in our study was low and appeared to be similar among study arms, although the incidence of gastrointestinal adverse effects may be related to LPV/r (43). However, it was not possible to accurately evaluate the relationship between adverse events related to LPV/r and LPV/r dosing, due to the reduced frequencies of these events.

In our study, the maternal blood level of LPV measured in the standard-dose group (3.5 μg/ml) was lower than the value reported by Else and colleagues (24) for 6 cases (4.5 μg/ml), but the values we reported were similar to the ones reported in this same

study for LPV cord blood levels (0.6 μg/ml) and RTV maternal and cord blood levels (0.32 and 0.31 μg/ml), although the time from the last LPV/r dose to delivery was longer in our study than in the previously cited studies (8.6 and 3.7 h, respectively). In an evaluation of 26 pregnant women who received the increased dose of LPV/r in the third trimester, the LPV levels in the maternal and cord blood were 5.2 μg/ml and 1 μg/ml, respectively (19). These findings suggest that the increased LPV/r dose did not provide a significantly higher exposure or increased probability of toxicity, nor was there an additive effect on PMTCT. Furthermore, the LPV cord blood and maternal ratios (C/M) were similar to the values published in recent trials, with C/M values of 0.17 (24) and 0.20 (19), indicating that increased doses of LPV do not result in greater placental transfer of LPV or RTV.

In conclusion, a standard dose of LPV/r yielded appropriate exposure for wild-type virus in the second and third trimesters of pregnancy in cART-adherent participants; however, the C_{min} and AUC values were lower than both the mean postpartum and nonpregnant adult values. The exposure associated with the standard LPV/r dose was insufficient to achieve the target levels necessary for HIV with PI resistance mutations. Although the clinical significance of this result is unclear, an increased dose during pregnancy may be considered for HIV-infected pregnant women who harbor resistance mutations.

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