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A Comparison of the Pharmacokinetics of Standard and Increased Dosage Lopinavir/Ritonavir Co-formulation Tablets in HIV-positive Pregnant Women: a randomized clinical trial

Pharmacokinetics of LPV/r in HIV Pregnant Women

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ABSTRACT

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 HIV-infected pregnant women between gestational weeks 14 and 30. Participants received either the standard (400/100 mg BID) or increased dose (600/150 mg BID) of LPV/r tablets during pregnancy and the standard dose for six weeks after childbirth. Pharmacokinetic 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 6.1µg/mL in the second and the third trimesters and postpartum, respectively. The increased dose group exhibited values of 7.9, 6.9 and 9.2 µg/mL at the same timepoints. 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%, 25% and 0%, 15%, 0% of the participants in the standard and increased dose groups, respectively, failed to achieve therapeutic levels against resistant viruses during the second and third trimesters and after childbirth. 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 an increased dose may be necessary for women harboring resistant HIV (*clinicaltrials.gov* identifier NCT00605098).

INTRODUCTION

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 (3,4).

Pharmacokinetic parameters may affect drug efficacy and toxicity (5). However, few studies have investigated the pharmacokinetic 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) plasma levels are higher in women (10-12), although PI exposure decreases during pregnancy, especially in the third trimester (13).

The use of lopinavir, co-formulated 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 pharmacokinetic 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 RTV, by comparing two different LPV/r doses (standard and increased) in pregnant women.

METHODS AND MATERIALS

Trial design and participants

This was a randomized, open-label prospective study (*clinicaltrials.gov* identifier NCT00605098) conducted at the Instituto de Pesquisa Clínica Evandro Chagas (IPEC),

Fundação Oswaldo Cruz (Fiocruz), that enrolled 60 HIV-infected pregnant women between 14-30 gestational weeks from two clinical sites in the Rio de Janeiro Metropolitan area: the STD/AIDS Service of Hospital Geral de Nova Iguaçu (HGNI) and the Infectious Diseases Service of Hospital dos Servidores do Estado do Rio de Janeiro (HSE). 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 BID) or increased dose (600/150 mg BID) of LPV/r tablets (Kaletra, Abbott Laboratories, Abbott Park, IL, 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 14-30 weeks, HIV-infected and intended to continue 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 an informed consent (IC) prior to study enrolment.

HIV-1 viral load, T-lymphocyte subpopulations, Complete Blood Count (CBC), Chemistry, Alanino aminotransferase (ALT), Aspartato aminotransferase (AST) and lipids were evaluated at baseline and at quarterly visits.

Concomitant medication use was evaluated at each study visit. Adverse events (AE) 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 Pharmacokinetic Sample Collection

Pharmacokinetic evaluations were performed at least two 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 enrolment. 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 hours thereafter. Umbilical cord and maternal blood samples (10 mL) were drawn at birth to evaluate transplacental drug delivery. At each pharmacokinetic evaluation, the time of the last LPV/r dose was also recorded. Blood samples were centrifuged at 4,000 rpm for 10 minutes, and each plasma supernatant sample was aliquoted and stored at -70°C until assayed.

Analytic Method

The LPV and RTV plasma levels 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 10-1000 ng/mL and 2-300 ng/mL, respectively.

Pharmacokinetic Analysis

Phoenix WinNonlin® software (version 6.2.1) was used to determine the area under the curve until the last measurable concentration ($AUC_{[0-12]}$), plasma drug concentration at 12

h (C_{12h}), peak drug concentration (C_{max}), minimum drug concentration (C_{min}), pre-dose concentration (C_{pd}), total apparent oral clearance (Cl/F), time to C_{max} (t_{max}) and time to C_{min} (t_{min}) by non-compartmental 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 pharmacokinetic parameters $AUC_{[0-12]}$, C_{min}, C_{12h}, C_{max}, C_{pd}, Cl/F, t_{max} and t_{min}. Maternal viral load 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 primary endpoints was performed only for the cART-adherent population at each PK evaluation moment. cART adherent was defined according to the following criteria: >80% adherence according to pill counts, adherence of 100% according to patient self-reports and LPV $C_{pd} > 0.2$ µg/mL, the plasma level used as a marker of non-adherence in previous therapeutic drug monitoring studies (12). Efficacy and safety endpoints were described for all participants who participated in at least one pharmacokinetic 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 alpha of 0.05. A drop-out 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 participants, 53 participated in at least one pharmacokinetic evaluation visit (Figure 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. Mean age at baseline was 27 years, and the mean gestational age at enrollment was approximately 20 weeks. Mean CD4+T-cell count was 536 cells/mm^3. Forty-seven HIV+ 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 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 co-formulated 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 I.V. during delivery, and 53/54 infants (98%) received ZDV P.O. for six weeks.

Pharmacokinetic analysis

Clinical data (treatment adherence, weight, gestational age and time between the last dose and the first sample drawn for pharmacokinetic evaluation) and the pharmacokinetic 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 media LPV and RTV plasma concentrations among pregnant women who received the standard and increased doses of LPV/r are shown in Figures 2 and 4, respectively. The Figure 3 compares the media plasma 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_{12h} were significantly different in the two arms (Table 3). At the second trimester and postpartum assessments, all participants in both arms who were considered adherent to cART (Figure 1) presented a $C_{min} > 1$ µg/mL, which is the recommended efficacy threshold to block virus replication. At the third trimester assessments, one participant in each arm exhibited $C_{min} < 1$ µg/mL. At the second trimester and postpartum assessments, all participants receiving the increased dose of LPV/r exhibited $C_{min} > 4$ µg/mL, which is the therapeutic level considered effective for resistant viruses (27, 28). Conversely, in the LPV/r standard dose group, 10/20 (50%) and 5/20 (25%) participants presented a $C_{min} < 4$ 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 standard and increased LPV/r dose arms, respectively, exhibited C_{min} values 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 $AUC_{[0-12]} < 52$ h.µg/mL, which is within the 10th percentile of $AUC_{[0-12]}$ based on data from non-pregnant adults. This participant was adherent

197 to cART but presented a Cl/F of 11.7 L/h, which is superior to the mean value observed for
198 the standard dose group at the third trimester (4.9 L/h).

199 The LPV mean pharmacokinetic parameters C_{max}, $AUC_{[0-12]}$, t_{min}, C_{12h} and Cl/F
200 during pregnancy were significantly different than those at the postpartum visit ($p<0.01$),
201 particularly for the LPV/r standard dose group, indicating that the increased LPV/r dose is
202 associated with a greater similarity in the pharmacokinetic parameters during pregnancy and
203 postpartum (Table 3). This difference was sustained even 4 weeks after delivery, when
204 participants in both arms received the LPV/r standard dose.

205 The minimum RTV concentrations for adherent participants were 90.2, 106.4 and
206 190.2 ng/mL for the standard dose arm and 205.8, 182.5 and 241.3 ng/mL for the increased
207 dose arm in the second trimester, third trimester, and postpartum, respectively. The RTV
208 $AUC_{[0-12]}$, C_{min}, C_{pd}, C_{max} and C_{12h} during pregnancy were significantly lower than those
209 at the postpartum visit ($p<0.04$), especially for the standard LPV/r dose group.

210 **Transplacental LPV and RTV levels**

211 When 12 participants from the standard dose arm and 7 participants from the
212 increased dose arm were evaluated, the mean LPV maternal plasma levels at delivery were
213 3.5 µg/mL and 4.0 µg/mL (with samples drawn 8.6 and 7.6 hours after the last LPV/r dose),
214 respectively. From the standard dose arm and the increased dose arm, the mean cord blood
215 LPV levels were 0.7 and 1.0 µg/mL, and the mean cord blood/maternal plasma ratios were
216 0.20 and 0.18, respectively. At delivery, the mean RTV concentrations were 192.8 and 147.5
217 ng/mL in the maternal blood and 16.8 and 35.8 ng/mL in the cord blood for the standard and
218 increased dose arms, respectively. No significant difference in LPV and RTV transplacental
219 passage was detected between the two arms ($p=0.67$ and $p=0.81$, respectively).

220 **Virologic response**

After 4 weeks on study, the participants in both arms had a progressively higher CD4+ T-cell count and almost 80% of parents had an undetectable viral load, including in those subjects deemed non-adherent. Only 9 participants presented a detectable HIV RNA viral load after 4 weeks of treatment, four were considered non-adherent, 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). Grades 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 and 26 from the increased dose arms mothers. There were 4 premature deliveries (7.6%), 2 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 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: 2 cases of haemangioma (1 in each arm) and 3 cases of inguinal hernias (1 from the standard dose arm and 2 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 two months of life and aspiration pneumonia at three months of life, respectively. The consent was withdrawn before the end of the study for 2 neonates (1 from each arm). All of the remaining 49 infants evaluated were uninfected.

DISCUSSION

In the present study, we compare the pharmacokinetic 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 pharmacokinetic parameters during pregnancy and after delivery. LPV AUC values in the increased dose arm were higher than AUC reported for non-pregnant adults (29), but were consistent with pharmacokinetic parameters determined in non-Caucasian adults with low body weight (30). Even producing a lower LPV exposition 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 non-pregnant adults (29). After delivery, LPV AUC of 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 exposition was similar only in the postpartum, when AUC and Cmax did not differ significantly.

The lower LPV/r exposition during pregnancy demonstrated by our and other previously studies (19, 24, 34) was probably related to bioavailability and Cl/F alterations in this period. In our study, Cl/F was higher during pregnancy, when compared to postpartum, specially 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 L/h in second and third trimester and at postpartum (19). In other study with pregnant women receiving LPV soft-gel capsules, the media Cl/F value was 9 L/h at antepartum and decreased to 6.1L/h at postpartum (30).

All adherent participants had AUC and C_{min} values above the target values, with the exception of one participant. A LPV C_{min} below 1 µg/mL (minimum effective concentration in treatment-naïve adult HIV 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 LPV/r standard dose and considered adherent to the treatment exhibited mean LPV C_{min} similar to those observed for pregnant women in Thailand (22), the US (33) and the United Kingdom (24) (Table 6). Participants from these studies had weights similar to our study participants.

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 participant and those from the previously cited studies. One of the limitations of TDM studies is that only pre-dose 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.

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 pharmacokinetic 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 two 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 vs. 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 non-pregnant adults.

Best and colleagues (19) conducted a study in pregnant women using LPV/r standard dose during second trimester and postpartum, and increased dose (6 pills a day) during 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 gelatine capsules (30). 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 Cmin < 1 µg/mL. Participants receiving an LPV/r increased dose at the third trimester had a Cmin 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 Cmin of 1 µg/mL (19). In our study, the adherent participants achieved Cmin (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 (35). 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 US and European studies were predominantly black, whereas 44.4% of the women in our study population self-identified as white. Pharmacogenetic characteristics related to ethnicity can affect the pharmacokinetics of some drugs (36, 37), as has already been demonstrated in studies evaluating the pharmacokinetics and pharmacogenetics of LPV in adults and children from the US (38, 39). Correlating pharmacogenetic studies with race and ethnicity can cause misinterpretation (40), especially in Brazil, where the genetic characteristics reflect miscegenation among Amerindians, Europeans and Africans (41). 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 (42). 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, 30, 43).

In addition, the high inter-individual variability in PI plasma levels, which is approximately 34% for the LPV/r tablet formulation (44), 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 pharmacokinetic parameters reported by different studies. In our study, inter-individual 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 non-pregnant adults.

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 non-pregnant adults (5.5 µg/mL) (44), 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 non-pregnant adults (92.6 h.µg/mL). These results confirm our finding that the LPV exposure during pregnancy in the standard dose group was lower than that for non-pregnant 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 $C_{min} > 4$ µg/mL in the second trimester and postpartum, and 85% Cmin > 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 vs. 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 pharmacokinetic 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 (45). 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 pharmacokinetic 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 previously studies (19, 20, 22, 24, 44). These results demonstrate that the RTV exposure of pregnant women receiving a standard dose of LPV/r is similar to that of non-pregnant adults and most likely not responsible for the decreased LPV exposure during pregnancy.

The LPV/r efficacy of the standard dose 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 was comparable to other reported results (21, 22, 24, 33); none of the babies evaluated (49/54) was infected.

The treatments safety evaluation indicated that LPV/r standard and increased dose 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 (44). 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 (8.6 and 3.7 hours, respectively). In an evaluation of 26 pregnant women who received the LPV/r increased dose at 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,

419 the LPV cord blood and maternal ratios (C:M) were similar to the values published in recent
420 trials, with C:M values of 0.17 (24) and 0.20 (19), indicating that increased doses of LPV do
421 not result in greater placental transfer of LPV or RTV.

422 In conclusion, a standard dose of LPV/r yielded appropriate exposure for wild-type
423 virus in the second and third trimesters of pregnancy in cART-adherent participants;
424 however, the C_{min} and AUC values were lower than both the mean postpartum and non-
425 pregnant adult values. The exposure associated with the standard LPV/r dose was insufficient
426 to achieve the target levels necessary for HIV with PI-resistance mutations. Although the
427 clinical significance of this result is unclear, an increased dose during pregnancy may be
428 considered for HIV-infected pregnant women who harbor resistance mutations.
429

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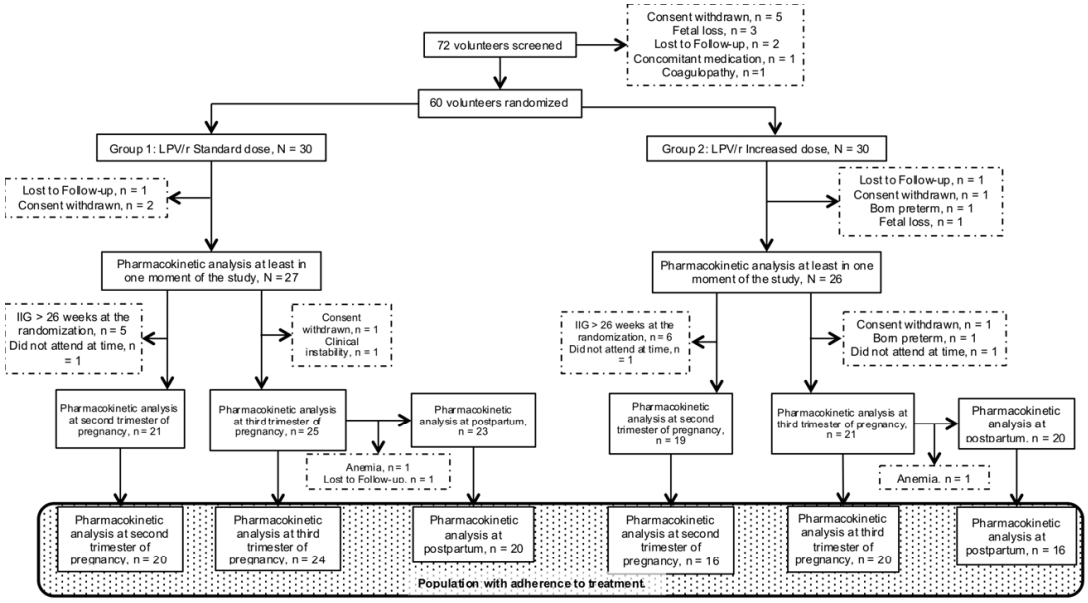

Figure 1. Patient Flowchart

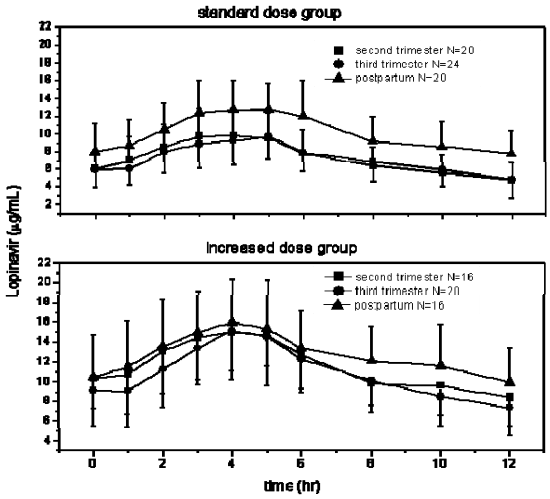

Figure 2 – Mean LPV plasma concentration according to LPV/r dose, evaluation timepoint (second and third trimester of pregnancy and post-delivery) for the cART-adherent population at each PK evaluation moment – mean (SD).

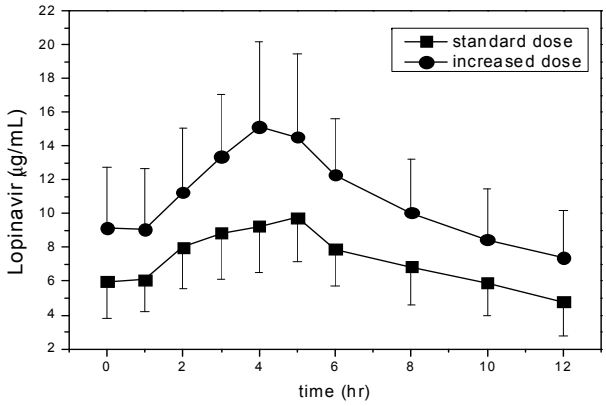

Figure 3 – Mean LPV plasma concentration to LPV/r standard and increased doses during third trimester of pregnancy for the cART-adherent population – mean (SD).

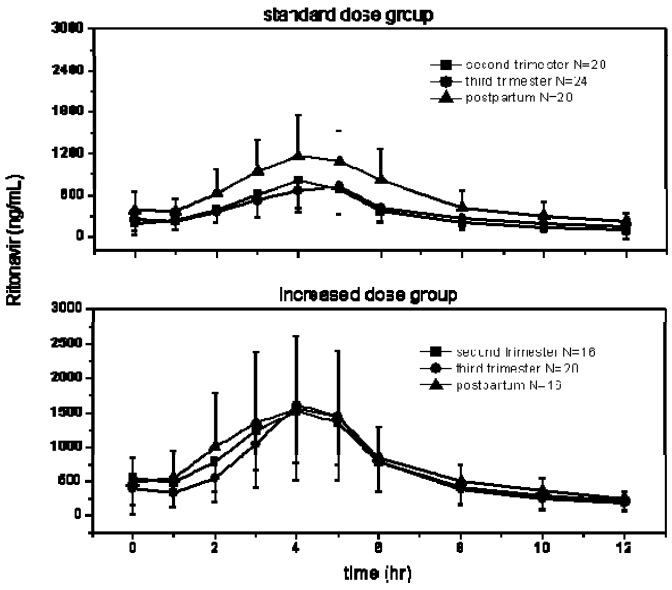

Figure 4 – Mean RTV plasma concentration according to LPV/r dose, evaluation timepoint (second and third trimester of pregnancy and post-delivery) for the cART-adherent population at each PK evaluation moment – mean (SD).

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

	PV/r standard dosing (n = 27)	**LPV/r increased dosing (n = 26)**	**Total (N = 53)**
Age (years); Mean (SD)	27.7 (5.7)	26.6 (5.7)	27.2 (5.7)
Gestational age (weeks); Mean (SD)	19.5 (5.6)	20.5 (5.7)	20.0 (5.7)
Weight (kg); Median (IQR)	61.7 (56.1 – 68.9)	58.9 (56.3 – 71.5)	60.1 (56.1– 70.3)
ARV naïve; n (%)	20 (74)	18 (69)	38 (72)
Nadir CD4+ T-cells (cells/mm^3); Mean (SD)	509 (174)	493 (155)	498 (165)
CD4+ T-cells (cells/mm^3); Mean (SD)	521 (156)	553 (151)	537 (154)
HIV viral load (log10); Mean (SD)	3.5 (3.5)	3.6 (3.6)	3.6 (3.6)
Total time under study treatment (weeks); Mean (SD)	21.7 (6.5)	26.6 (5.7)	20.9 (6.8)

Table 2. 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 at postpartum for all patients who participated in at least one pharmacokinetic evaluation visit (n = 53)

	2th 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; n (%)	20/21 (96)	16/19 (92)	24/25 (97)	20/21 (95)	20/21 (92)	16/20 (90)
Gestational age or weeks after delivery; Mean	21.7	22.2	31.1	31.2	5.2	4.7
Weight (kg); Mean	65.7	66.8	68.2	67.9	66.4	64.6
Time (hours) between last dose and sample drawn; Mean	11.4	11.3	11.0	11.2	11.9	10.9

Table 3 – Pharmacokinetic parameters of Lopinavir and Ritonavir during the second and third trimesters of pregnancy and at postpartum for the cART-adherent population at each PK evaluation moment - mean (standard deviation)

	2th trimester of pregnancy			3th trimester of pregnancy			Postpartum		
	LPV/r standard dose (n = 20)	LPV/r increased dose (n = 16)	p-value (Wilcoxon)	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									
Tmax (h)**	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
Cmax (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 0-12hs (h*mcg/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
Tmin (h)**	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
Cmin (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 (L/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									
Tmax (h)**	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
Cmax (ng/mL)	873.4 (400.7)	1704.8 (760.2)	**0.001**	842.6 (383.1)	1762.0 (1095.1)	**< 0.001**	1419.0 (519.8)	1737.3 (1108.2)	0.85
AUC 0-12hs (h*ng/mL)	4127.9 (1541.3)	8495.7 (3619.6)	**< 0.001**	4326.9 (1359.9)	7810.2 (4145.5)	**0.002**	7264.0 (2545.4)	9441.1 (5274.4)	0.40
Tmin (h)**	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**
Cmin (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 (L/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

*Pharmacokinetic parameters of Lopinavir and Ritonavir of volunteers with adherence to treatment - media (standard deviation)

**Median (interquartile range)

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

Events	LPV/r standard dosing (n = 27)		LPV/r increased dosing (n = 26)	
	Total (%)	Related to LPV/r - n (%)	Total (%)	Related to LPV/r - n (%)
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

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

Events	Grade	LPV/r standard dosing (n = 27)	LPV/r increased dosing (n = 26)
Anemia	1	4 (14.9%)	3 (11.5%)
Increased ALT / AST	1	1 (3.7%)	0
Increased total cholesterol*	1	3 (11.1%)	4 (15.4%)
	2	2 (7.4%)	2 (7.7%)
Increased LDL*	1	3 (11.1%)	4 (15.4%)
	2	2 (7.4%)	2 (7.7%)
Increased triglycerides*	1	1 (3.7%)	2 (7.7%)
	2	2 (7.4%)	1 (3.9%)
Any abnormal result in urinalysis	-	7 (25.9%)	5 (19.2%)

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

Reference	Weight (Kg)	Cmin (µg/mL)			Cpd (µg/mL)		
		2nd trimester	3rd trimester	Postpartum	2nd trimester	3rd trimester	Postpartum
Present study	61.8-69.4	4.5	4.3	6.1	6.1	6.0	8.0
Khuong-Josses et al (2007) (18)	-	-	-	-	-	4.6	-
Lambert et al (2011) (21)	88 (49-103)*	-	-	-	3.5	3.3	5.1
Raumautarsing et al (2011) (22)	54.9/60.1/ 56.3**	2.4	3.2	4.7	-	-	-
Else et al (2012) (24)	77 (55-116)*	4.6	2.5	4.7	5.7	3.7	6.1
Patterson et al (2011) (33)	-	5.2	4.0	7.2	-	-	-

*values are given as median (range).

** at 2nd and 3rd trimester and postpartum.