A Randomized Controlled Trial to Assess Safety, Tolerability, and Antepartum Viral Load with Increased Lopinavir/Ritonavir Dosage in Pregnancy

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Abstract

HIV mother-to-child transmission (MTCT) is significantly reduced if antepartum viral load (apVL) is <50 copies/mL. Pharmacokinetic studies suggest increasing the dosage of lopinavir/ritonavir (LPV/r) in pregnancy. It is important to assess tolerance, safety, and rate of patients presenting a apVL <50 copies/mL when treating with increased dose of LPV/r during pregnancy. Confirmed HIV-infected pregnant women with a fetus at a gestational age of 14–33 weeks were randomly assigned to receive LPV/r 400/100 or 600/150 mg b.i.d. plus two nucleoside analogues (NRTIs). Treatment was discontinued in the case of alanine transaminase (ALT) of grade III elevation or higher, glucose, or triglycerides. Thirty-two women were randomized to the LPV/r 400/100 mg dose, and 31 women were randomized to the 600/150 mg dose. Overall, 9.4% of the women receiving the conventional dose, and 17.2% receiving the increased dose, discontinued treatment because of adverse events ($p=0.29$). The rates of gastrointestinal (GI) symptoms, laboratory abnormalities, preterm delivery, and low birth weight were similar in both groups. There were no cases of HIV MTCT. Among the women with a baseline VL >50 copies/mL assigned to the conventional dose group, 45% (95% confidence interval [CI] 62.5–27.5%) had a apVL >50 copies/mL compared with 10.5% (95% CI 21.6–0.6%) of those assigned to the increased dose group ($p=0.01$). There was no significant difference found for the patients with a baseline VL <50 copies/mL. In pregnant women with a baseline VL >50 copies/mL, it may be warranted to initiate LPV/r dosing at 600/150 mg, whereas the conventional dose is sufficient for pregnant women with a baseline VL <50 copies/mL.

Introduction

THE MAGNITUDE OF ANTEPARTUM VIRAL LOAD (apVL) is directly related to the rate of mother-to-child transmission (MTCT) of HIV-1.¹ An observational study found an 8% MTCT rate in pregnant women who received zidovudine monotherapy, a 3% rate for women who received dual antiretroviral therapy, and a 1.6% rate for women who received highly active antiretroviral therapy (HAART).² Other studies that have examined HAART observed rates of MTCT <0.4% if the patient apVL was <50 copies/mL.^{3,4} To achieve an undetectable viral load, all current recommendations for the management of HIV-infected pregnant women propose the use of HAART.^{5–7} Ritonavir-boosted lopinavir (LPV/r) is the protease inhibitor (PI) of choice for the treatment/prophylaxis of HIV-infected pregnant women.

Physiological changes during pregnancy can significantly alter LPV serum levels, especially in the third trimester, which

can compromise antepartum viral suppression and increase the risk of MTCT.^{8,9} Several pharmacokinetic studies have suggested that LPV/r dose should be increased during pregnancy, but there are no randomized clinical studies comparing conventional and increased doses of LPV/r during pregnancy.

The objective of the present study was to evaluate the safety, tolerability, and antepartum viral load with an increased dose of LPV/r during pregnancy, compared with a conventional dose, and to compare the rates of patients achieving an HIV RNA apVL of <50 copies/mL and the rates of adverse events affecting the pregnant women and their fetuses.

Methods

Study design

A computer algorithm was used to perform a block randomization with randomly selected block sizes of four and

six, to allocate pregnant women to equally receive either 400 mg lopinavir in combination with 100 mg ritonavir (conventional dose) or 600 mg lopinavir in combination with 150 mg ritonavir (increased dose), b.i.d., in combination with two nucleoside analogues (NRTIs) selected at the discretion of the attending physician. Clinicians were not blinded to treatment arm. This protocol was approved by the Committee for Ethics in Research of the Universidade Federal de São Paulo (UNIFESP) Medical School, Brazil. The study was conducted between August 2008 and January 2012 at the reference center for HIV-infected pregnant women at the UNIFESP Medical School, Brazil.

Participants

We enrolled 63 pregnant women with a confirmed HIV infection that had not previously shown resistance to LPV/r and with a fetus whose gestational age was between 14 and 33 weeks. These women agreed to participate by signing an informed consent form. Women with blood glucose levels > 126 mg/dL, triglycerides (TG) > 500 mg/dL, and alanine transaminase (ALT) > 2.5 times the upper limit of normality were excluded.

Intervention

After randomization, the pregnant women were evaluated monthly during pregnancy to monitor the occurrence of gastrointestinal (GI) symptoms (diarrhea, nausea, and vomiting) using a standardized questionnaire, changes in laboratory tests (TG, total and lipoprotein fraction cholesterol, fasting glucose, transaminases, creatinine, and bilirubin), CD4 count, and HIV-1 viral load. Gestational age and weight at delivery and antepartum viral load were assessed 15 days post-delivery. Following delivery, the LPV/r dose was reduced to the conventional dosing level for all of the pregnant women who had been receiving the increased dose level.

Study outcome and end-points

The primary outcome was an HIV RNA level < 50 copies/mL in samples collected during the last 4 weeks of pregnancy, as illustrated in Fig. 1. The patients were followed until delivery or withdrawal of informed consent, or until they were removed from the study because of grade III clinical symptoms (diarrhea, vomiting, or nausea) or laboratory abnormalities (glycemia, TG, ALT, or creatinine) according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events – DAIDS.¹⁰

Statistical analyses

The baseline characteristics of the increased and conventional LPV/r groups were compared using Student's *t* test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables. The rates of GI symptoms, laboratory abnormalities, preterm delivery, and low-birth weight were compared between the two groups using the χ^2 test. Variables including the LPV/r group associated with an antepartum viral load < 50 copies/mL by the univariate analysis were further analyzed using a logistic regression model. Differences with a *p* value of < 0.05 were interpreted as a statistically significant. SPSS software version 20 (IBM, Armonk, NY) was used for all statistical analyses.

Results

All 61 patients were randomized. Thirty-two patients received the conventional dose, and 31 received the increased dose. Two women in the increased dose group were excluded for protocol violations. The mean time of LPV/r use was 85 days for the conventional dose group (interquartile range [IQR] 62–112) and 86 days for the increased dose group (IQR 62.25–114.50), and eight and ten patients, respectively, had been already receiving LPV/r prior to the randomization. The baseline demographic, clinical, anthropometric, and laboratory characteristics of the two groups are shown in Table 1.

Grade II or III diarrhea occurred only during the first month of LPV/r use. In pregnant women who were using LPV/r prior to the randomization, there were no (0/8) cases of diarrhea in those randomized to receive the conventional dose, whereas 10% (1/10) of patients randomized to receive the increased dose presented grade III diarrhea, and 20% (2/10) presented grade II diarrhea in the 1st month. For the pregnant women who did not use LPV/r prior to the randomization, 25% (6/24) in the conventional dose group presented with grade I or II diarrhea, and 36.9% (7/19) in the increased dose group presented diarrhea (*p*=0.51). In the pregnant women who were not using LPV/r prior to randomization, grade I nausea was reported in the 1st month by 20.8% (5/24) of the patients receiving the conventional dose, and by 42% (8/19) of the patients receiving the increased dose (*p*=0.18). Among the patients who had been already receiving LPV/r prior to the randomization, only 5.5% (1/19) of the patients receiving the increased dose presented grade I nausea. There was no need to use anti-emetic medications, decrease in fluid and nutrient intake, or loss of weight.

None of the pregnant woman had blood glucose levels higher than grade I, two patients in the conventional dose group were excluded because their TG levels had risen to grade III, and one patient from each group was excluded because their ALT levels had increased to level III.

The incidence of preterm birth was 19.3% in the conventional dose group and 17.8% in the increased dose group (*p*=0.60).

The percentage of women with an HIV-1 antepartum viral load of less than 50 copies/mL was significantly higher in the increased dose group (89.7%; 95% confidence interval [CI]: 0.78–1%) than in the conventional dose group (68.8%; 95% CI: 0.52–0.84%) (*p*=0.04). In both groups, detectable antepartum VL ranged from 84 to 872 copies/mL. As recommended by the Brazilian Ministry of Health, all pregnant women received zidovudine during labor, irrespective of antepartum VL.

Among pregnant women with a baseline VL > 50 copies/mL at the time of randomization, the percentage of women with an apVL < 50 copies/mL at delivery was significantly higher in the patients assigned to the increased dose group (89.5%; 95% CI: 27.5–62.5%) than in the conventional dose group (55%; 95% CI: 0.6–21.6%) (*p*=0.01). However, in pregnant women with an undetectable baseline VL at randomization, there was no difference in the percentage patients with an undetectable apVL between the conventional dose group (8.3%; 95% CI: 0–0.17%) and the increased dose group (10%; 95% CI: 0–0.2%) (*p*=1.0), as illustrated in Fig. 2. There was no significant association among undetectable apVL and prior use of PI or body mass index (BMI). In

FIG. 1. CONSORT flow diagram.

addition to the grouping variable, VL at randomization and enfuvirtide use during pregnancy were also significantly associated with an undetectable apVL. However, in the logistic regression analysis that included these three variables in the model, only the receipt of the increased dose was independently associated with undetectable apVL levels (OR: 4.52, 95% CI: 1.01–20.4, $p=0.04$). There were no cases of HIV MTCT.

Discussion

This study compared the efficacy, safety, and tolerability of an increased dose of LPV/r administered during the second and third trimester of pregnancy with the conventional dose. The percentage of patients with an apVL <50 copies/mL receiving the higher dose (89.7%) was significantly higher than among the patients receiving the conventional dose (68.8%) ($p=0.04$). There was no significant difference in the adverse event rates related to diarrhea and nausea or in laboratory abnormalities between the two groups. Likewise, the preterm delivery rates associated with the higher dose (17.8%) and the conventional dose (19.3%) were similar ($p=0.6$).

apVL

Pregnant women with a baseline HIV-1 VL >50 copies/mL assigned to the higher LPV/r dose (10.5%) achieved a greater rate of VL ≤50 copies/mL at delivery than those assigned to the conventional dose (45%) group ($p=0.01$). In contrast, pregnant women with undetectable baseline VLs had a similar rate of VL ≤50 copies/mL at delivery ($p=1.0$).

The risk of MTCT is directly correlated with the antepartum HIV VL.¹¹ However, the threshold of apVL that can prevent MTCT remains uncertain. The current American recommendations for the use of antiretroviral drugs in pregnant HIV-1-infected women suggest a scheduled cesarean delivery at 38 weeks of gestation when the apVL is >1000 copies/mL or unknown, and also mandate intravenous zidovudine for women with an apVL >400 copies/mL.^{12–16} Therefore, should an apVL of 400 copies/mL be the optimal goal to minimize MTCT of HIV?

In the T-20 versus Optimized Regimen Only (TORO), Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST), and Performance Of TMC114/ritonavir When evaluated in

TABLE 1. BASELINE DEMOGRAPHIC, CLINICAL, ANTHROPOMETRIC, AND LABORATORY CHARACTERISTICS OF THE CONVENTIONAL DOSE AND INCREASED DOSE GROUPS

	Conventional dose (Group 1)	Increased dose (Group 2)	p
Number of patients	32	29	
Average age (years)	28.5	29.4	0.67
Average length of HIV infection (months)	76	64.9	0.46
Average CD4 (cells/mm ³)	475	531	0.41
Average viral load (copies/mL)	11.712 (IQR 25–4.929)	49.933 (IQR 25–3.836)	0.26
Detectable viral load at randomization (n)	20	19	1.0
Average BMI	24.85	25.16	0.72
On HAART at baseline (n/%)	21 (65%)	18 (62%)	0.79
Prior PI (n/%)	16 (50%)	16 (55%)	0.80
Kaletra use at randomization (n/%)	8 (25%)	10 (34.4%)	0.29
Diarrhea (n)			0.054
No	27	29	
Yes	5 (15.6%)	0 (0%)	
Nausea (n)			0.20
No	28	21	
Yes	4 (12.5%)	8 (27.5%)	
Vomiting (n)			1.0
No	30	28	
Yes	2 (6.25%)	1 (3.4%)	
Glycemia (mg/dL)	80	78	0.32
Basal insulin (μ UI/mL)	6.8	6.5	0.87
HOMA-IR	1.4	1.24	0.57
TG (mg/dL)	193	186	0.75
ALT (mg/dL)	14	11	0.33
TC (mg/dL)	186	185	0.97
HDL-c (mg/dL)	57	56	0.74
LDL-c (mg/dL)	90	95	0.54
Creatinine (mg/dL)	0.53	0.52	0.68

BMI, body mass index; HAART, highly active antiretroviral therapy; HOMA-IR, Homeostasis Model of Assessment - Insulin Resistance; TG, triglycerides; ALT, alanine transaminase; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

Treatment-Experienced patients with PI resistance (POWER) trials, an HIV RNA <50 copy end-point demonstrated the strongest durability over time, whereas HIV RNA levels <400 copies/mL were less sustainable over 48 weeks of treatment.¹⁷ Clinical trials of new antiretroviral drugs in highly experienced patients also presented high rates of HIV-RNA suppression <50 copies/mL. Subsequently, HIV RNA level suppression <50 copies/mL has become the standard efficacy end-point across trials of both naive and experienced patients. However, the ideal HIV RNA level threshold could be even lower. In 2012, a study analyzed 1247 non-pregnant patients on ART with a VL <50 copies/mL, and found that patients with viral loads of 40–49 copies/mL or those with viral loads <40 copies/mL but with a positive qualitative RNA test were at a greater risk of a sustained VL increase.¹⁸

These findings suggest that tests with lower limits of detection should be used to assess the efficacy of the response to ART, which is extremely relevant for the treatment and/or prophylaxis of HIV-infected pregnant women. In addition, a case of HIV MTCT in which the mother had a VL <400 copies/mL was recently described.¹⁹ This patient had a 239 copy/mL level during delivery, and the transmission occurred during the antepartum period. The newborn was HIV RNA-negative at 2 and 10 days, and tested positive at 1 month old.

A retrospective study conducted in England and Ireland between 2000 and 2006 with HIV-infected pregnant women found an MTCT rate of 0.1% among women with a apVL of <50 copies/mL, whereas the rate was 1.2% among women with apVLs between 51 and 999 copies/mL.⁴

A study conducted in France with >5000 HIV-infected pregnant women who used ART during pregnancy and did not breastfeed found a 0.7% MTCT rate for women with apVLs between 401 and 999 copies/mL, a 0.6% rate (95% CI 0.3–1.0%) for women with apVLs <400 copies/mL, and a rate of <0.4% (5/1338; 95% CI 0.1–0.9) for women with <50 copies/mL at delivery.³ In addition, 57% of the MTCT events from the women with a VL <400 copies/mL at delivery occurred during the antepartum period.

The 2012 British guidelines for the management of HIV infection in pregnant women recommend vaginal delivery for women using HAART with a VL <50 copies/mL at 36 weeks of gestation, and elective cesarean delivery for women with a VL >400 copies/mL independent of ART use. In women with loads between 50 and 399 copies/mL, elective cesarean delivery should be considered.⁶

The abovementioned considerations underscore the need for the lowest possible limit of HIV RNA detection at delivery to minimize MTCT.

Pregnant women with a VL <50 copies/mL at the time of randomization did not need to receive an increased dose of

FIG. 2. Rates of peripartum HIV RNA level >50 copies/mL among pregnant women treated with a conventional and increased dose of lopinavir/ritonavir according to baseline HIV RNA level.

LPV/r to maintain an undetectable apVL at delivery. The concentration of LPV/r required to achieve an apVL <50 copies/mL is likely greater than that needed to maintain a VL <50 copies/mL. The evidence suggests that the risk of virological failure is 10-fold lower in patients with a VL <50 copies/mL for >72 months than in patients with a VL <50 copies/mL for <12 months.²⁰ This study suggests that individuals with long-term viral suppression may be able to miss more doses (resulting in lower drug concentration) without experiencing viral rebound.

GI events

None of the pregnant women who were using LPV/r at the time of randomization and who were assigned to receive the conventional dose had diarrhea, most likely because they were already adapted to this medication. In contrast, those assigned to receive the increased dose had similar rates of diarrhea as the pregnant women who started ART with the conventional dose or increased dose during pregnancy: 30%, 25%, and 36.9%, respectively. Nausea, although it was more frequent in the increased dose group, was well tolerated, and there was no need to use anti-emetic medications, decrease in fluid and nutrient intake, or loss of weight. When using the conventional dose of LPV/r in men and non-pregnant women, diarrhea occurs in 39–57% of patients and nausea occurs in 11–15% of patients during the 1st year.^{21,22} Among patients who were exposed to HIV while receiving a prophylactic ART regimen with LPV/r at the conventional doses of tenofovir and emtricitabine, there was a 78% incidence of diarrhea and 59% incidence of nausea during the first 28 days of use.²³ The lower rates of occurrence of diarrhea during pregnancy may be attributed to the constipation that occurs during pregnancy because of the progestational effect.²⁴

Changes in laboratory tests

There was no notable increase in the blood glucose level of the pregnant patients evaluated despite evidence that suggests that there is an increased risk of gestational diabetes with the use of PIs.^{25,26}

The use of the increased dose of LPV/r was not associated with a significant increase in total cholesterol (TC) or TG

compared with the conventional dose. Hypertriglyceridemia and hypercholesterolemia have been reported in patients treated with the conventional dose of LPV/r.^{21,27} However, during pregnancy, there is an increase of TG in the first trimester.²⁸ Lipids are used as an energy source for the fetus, and as precursors for bile acids and steroid hormones. Increased TG levels can be notably high independent of ART use.^{29,30}

An increase in ALT levels was rarely observed in the present study. One patient using the increased dose presented with hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome during her pregnancy. One patient in the conventional dose group was excluded for having elevated asymptomatic grade III ALT levels. Pivotal studies on LPV/r have shown that increased ALT levels occur in ~2% of patients.^{31,32}

Prematurity

The occurrence of preterm delivery in the increased dose group (17.8%) was similar to that of the conventional dose group (19.3%). Recently, a study evaluating 1869 singleton births in the United States found that of 18.6% of preterm births, 10.2% were spontaneous.³³ Additionally, the odds of preterm birth and spontaneous preterm birth were significantly greater among mothers who used PIs in the first trimester but not among mothers who used non-nucleoside reverse transcriptase inhibitors or triple nucleoside regimens during the first trimester. Individual PIs associated with a preterm birth were saquinavir, zidovudine, and LPV/r. The authors note that the mechanism of the first trimester effect is unclear, but could be related to changes in immune and inflammatory mediators. Further studies are needed to elucidate the specific drug effects and the interaction of the many factors that determine pregnancy outcome. Other published studies have determined an ~20% rate of preterm birth among women using PIs.^{34–36}

Conclusions

Compared with the conventional dose, the increased dose of LPV/r 600/150 mg was not associated with a greater frequency of GI symptoms, laboratory abnormalities, preterm delivery, or low birth weight. In pregnant women with a

baseline VL > 50 copies/mL, the dose of 600/150 mg of LPV/r seems warranted, whereas it does not seem necessary for those with a baseline VL < 50 copies/mL.

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Author Disclosure Statement

No competing financial interests exist.

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