Lopinavir/ritonavir dosing during pregnancy in Brazil and maternal/infant laboratory abnormalities

ABSTRACT

Objectives: To describe laboratory abnormalities among HIV-infected women and their infants with standard and increased lopinavir/ritonavir (LPV/r) dosing during the third trimester of pregnancy. **Methods:** We evaluated data on pregnant women from NISDI cohorts (2002-2009) enrolled in Brazil, who received at least 28 days of LPV/r during the third pregnancy trimester and gave birth to singleton infants. **Results:** 164 women received LPV/r standard dosing [(798/198 or 800/200 mg/day) (Group 1)] and 70 increased dosing [(> 800/200 mg/day) (Group 2)]. Group 1 was more likely to have advanced clinical disease and to use ARVs for treatment, and less likely to have CD4 counts ≥ 500 cells/mm^3. Mean plasma viral load was higher in Group 2. There were statistically significant, but not clinically meaningful, differences between groups in mean AST, ALT, cholesterol, and triglycerides. The proportion of women with Grade 3 or 4 adverse events was very low, with no statistically significant differences between groups in severe adverse events related to ALT, AST, total bilirubin, cholesterol, or triglycerides. There were statistically significant, but not clinically meaningful, differences between infant groups in ALT and creatinine. The proportion of infants with Grade 3 or 4 adverse events was very low, and there were no statistically significant differences in severe adverse events related to ALT, AST, BUN, or creatinine. **Conclusion:** The proportions of women and infants with severe laboratory adverse events were very low. Increased LPV/r dosing during the third trimester of pregnancy appears to be safe for HIV-infected women and their infants.

Keywords: pregnancy; HIV; HIV protease inhibitors; drug toxicity.

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INTRODUCTION

Mother-to-child transmission (MTCT) is the primary means by which children acquire HIV infection. Development and implementation of efficacious interventions to prevent MTCT (including antiretroviral [ARV] prophylaxis, cesarean section before labor and before rupture of membranes, and complete avoidance of breastfeeding), along with use of antiretroviral treatment by HIV-infected pregnant women who meet criteria for treatment, have resulted in the virtual elimination of MTCT in several areas of the world.[1]

Several national guidelines recommend combination antiretroviral regimens for prevention of MTCT of HIV and for the treatment of maternal HIV infection itself.[2-4] The combination of zidovudine (ZDV), lamivudine (3TC), and lopinavir/ritonavir (LPV/r) has become a common ARV regimen for prevention of MTCT of HIV in Brazil and other countries.

In our analysis of data from The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal Protocol, we examined the association between maternal ARV regimens used during pregnancy and infant preterm birth and low birth weight.[5] Although use of a protease inhibitor-containing regimen during pregnancy was not associated with an increased risk of these adverse infant outcomes, we emphasized the importance of monitoring HIV-infected women and their children for potential adverse events associated with maternal use of ARVs during pregnancy. Recently, McArthur *et al.*[6] reported twin preterm neonates with cardiac toxicity related to LPV/r. The twins were born preterm (32 weeks gestation) to an HIV-infected mother. One of them developed complete heart block and dilated cardiomiopathy, while the other developed mild bradycardia.

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During pregnancy, changes in drug pharmacokinetics are induced through physiological variations.[7-12] Increased progesterone levels tend to affect drug absorption, which also may be impaired by higher gastric pH. Drug distribution is modified by elevated body water and fat, while increased renal blood flow may enhance the clearance of some drugs. Plasma albumin and alpha-acid glycoprotein concentrations are decreased, potentially affecting protein binding. There may be concomitantly increased distribution, metabolism and excretion.[13] Finally, the expression of cytochrome P-450 is highly variable during pregnancy,[14] with potential consequences for the metabolism of many drugs, including protease inhibitors (PIs). Transplacental passage of PIs is generally low and cord blood PI concentrations are undetectable in most infants born to mothers receiving PIs.[15]

Plasma concentrations of LPV/r are reduced during the third trimester of gestation [Area Under the Curve (AUC) and trough levels (C_{min})].[7-10,12] Thus, an increase in LPV/r dose during the third trimester for both LPV/r-experienced and -naïve HIV-infected pregnant women or serum therapeutic drug monitoring (TDM)[2-3,12] have been endorsed by some experts. In a recent United States-based study, Best *et al.*[16] suggested that the higher LPV/r dose should be used in second and third trimester pregnant women, especially those who are PI-experienced, and that postpartum LPV/r dosing can be reduced to standard dosing within two weeks after delivery. However, higher dosing during the third trimester could be associated with the development of toxicities affecting both mother and infant, leading to lower adherence. There is limited information regarding maternal and infant adverse events with higher third trimester dosing. The objective of this study was to describe the occurrence of laboratory adverse events according to standard and increased LPV/r dosing during the third trimester of pregnancy in HIV-infected women and their infants.

MATERIAL AND METHODS

The study population comprised HIV-infected pregnant women enrolled in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal or Longitudinal Study in Latin American Countries (LILAC) protocols, who received LPV/r during the third trimester of pregnancy, and their infants. The NISDI Perinatal and NISDI LILAC protocols are prospective cohort studies that enrolled HIV-infected pregnant women and their infants at multiple sites in Argentina, the Bahamas, Brazil, Jamaica, Mexico, and Peru beginning in 2002 (NISDI Perinatal) and in 2008 (NISDI LILAC).[17] Participant follow-up continued for at least six months after delivery/birth (last maternal laboratory assays obtained at 6-12 weeks postpartum in the NISDI Perinatal Protocol). Choice and dosing of ARVs was at the discretion of each subject's physician. All women enrolled in the studies provided written informed consent, and the protocols were approved at local institutional review boards (IRBs), as well as the IRBs at NICHD and Westat.

Since the majority (61%) of the NISDI/LILAC enrollments occurred in Brazil and few subjects at sites in the other countries used increased dosing of LPV/r, data were only analyzed for participants from Brazil. Other inclusion criteria were: enrolled through December 31st, 2009; first on-study pregnancy; known pregnancy outcome that was a singleton birth; reached the third trimester of pregnancy; used LPV/r in the third trimester for at least 28 days; and received LPV/r standard [798/198 mg/day (soft gel capsules) or 800/200 mg/day (hard capsules)] or increased doses (> 800/200 mg/day) during the third trimester.

Maternal and infant adverse events were assessed according to standard or increased LPV/r dosages during the third trimester. Statistical analyses for categorical comparisons were performed using the Fisher's exact test and the Student's *t* test for comparison of means. Analyses were performed using SAS statistical software version 9.1; p-values < 0.05 were considered to be significant.

RESULTS

Overall, 1,630 pregnancies occurred among women enrolled in the cohorts through the end of 2009, 1,000 of whom were from Brazil. Of these, 966 women were enrolled for the first time and had known pregnancy outcomes. Of the 966 subjects, 944 used ARVs during the third trimester of pregnancy and had singleton births. Of these, 291 used LPV/r during the third trimester, and 234 subjects received standard or increased doses of LPV/r for at least 28 days. Therefore, the study population comprised 234 HIV-infected women and their infants. Of the 234 women, 164 (70.1%) used standard LPV/r dosing (Group 1) (median duration of use: 76 days) and 70 (29.9%) used increased dosing (Group 2) (median duration of use: 67 days).

Maternal variables are presented in Tables 1 and 2. Mothers in Group 1 were older than those in Group 2 (p = 0.002). A larger proportion of women in Group 1 compared to Group 2 were classified as CDC clinical disease stage B/C at both enrollment and hospital discharge (p = 0.0008 and p = 0.002, respectively). A larger proportion of mothers in Group 1 received ARVs for treatment (vs. prophylaxis) than in Group 2 (p = 0.02). A smaller proportion of women in Group 1 than Group 2 had CD4 counts of 500 cells/mm^3 or more at enrollment (p = 0.04) (Table 1). Although the proportion of subjects with a CD4 count at enrollment of 500 cells/mm^3 or more differed by group, the mean CD4 count did not differ between groups at enrollment or at hospital discharge (p > 0.2) (Table 2), and, although the

Table 1. Maternal categorical variables by LPV/r dosing group

Characteristic	Standard dosing (Group 1) n = 164 (%)	Increased dosing (Group 2) n = 70 (%)	p-value
Age at delivery (years)			
≤ 29	80 (48.8)	50 (71.4)	0.002
>29	84 (51.2)	20 (28.6)	
Education (completed years)			
0-6	54 (32.9)	23 (32.9)	1.00
7+	110 (67.1)	47 (67.1)	
Number of people in household			
1-3	79 (48.2)	36 (51.4)	0.67
≥ 4	85 (51.8)	34 (48.6)	
Gainful employment outside the home			
Yes	65 (39.6)	20 (28.6)	0.14
No	99 (60.4)	50 (71.4)	
Tobacco use during pregnancy			
Yes	47 (28.7)	21 (30.0)	0.88
No	117 (71.3)	49 (70.0)	
Alcohol use during pregnancy			
Yes	35 (21.3)	11 (15.7)	0.37
No	129 (78.7)	59 (84.3)	
Cocaine use during pregnancy			
Yes	8 (4.9)	1 (1.4)	0.29
No	156 (95.1)	69 (98.6)	
Marijuana use during pregnancy			
Yes	5 (3.0)	3 (4.3)	0.70
No	159 (97.0)	67 (95.7)	
Any substance use during pregnancy			
Yes	63 (38.4)	25 (35.7)	0.77
No	101 (61.6)	45 (64.3)	
CDC clinical disease stage at enrollment			
A	129 (78.7)	67 (95.7)	0.0008
B or C	35 (21.3)	3 (4.3)	
CDC clinical disease stage at hospital discharge			
A	128 (78.0)	66 (94.3)	0.0021
B or C	36 (22.0)	4 (5.7)	
Reason for ARV use during pregnancy			
Prophylaxis	71 (45.5)	43 (62.3)	
Treatment	85 (54.5)	26 (37.7)	0.02
*Missing**	8	1	
CD4 count at enrollment (cells/mm^3)			
<500	100 (61.0)	32 (45.7)	0.04
≥500	64 (39.0)	38 (54.3)	
CD4 count at hospital discharge (cells/mm^3)			
<500	75 (46.9)	26 (40.6)	
≥500	85 (53.1)	38 (59.4)	0.46
*Missing**	*4*	*6*	
Plasma viral load at enrollment (copies/mL)			
< 1,000	112 (71.8)	53 (75.7)	
≥ 1,000	44 (28.2)	17 (24.3)	0.63
*Missing**	*8*	*0*	

(Cont.)

Table 1. Maternal categorical variables by LPV/r dosing group

Characteristic	Standard dosing (Group 1) n = 164 (%)	Increased dosing (Group 2) n = 70 (%)	p-value
Plasma viral load at hospital discharge (copies/mL)			
< 1,000	137 (87.8)	53 (84.1)	
≥ 1,000	19 (12.2)	10 (15.9)	0.51
*Missing**	*8*	*7*	
CD4 count increase (enrollment to hospital discharge) (cells/mm³)			
Yes	109 (68.1)	47 (73.4)	
No	51 (31.9)	17 (26.6)	0.52
*Missing**	*4*	*6*	
Plasma viral load decrease (enrollment to hospital discharge) (copies/mL)			
Yes	48 (31.6)	22 (34.9)	
No	104 (68.4)	41 (65.1)	0.64
*Missing**	*12*	*7*	
ALT at enrollment (IU/L)			
≤ Grade 2	162 (100.0)	70 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*2*	*0*	
ALT at 6-12 weeks postpartum (IU/L)			
≤ Grade 2	161 (99.4)	68 (100.0)	
Grade 3/4	1 (0.6)	0 (0.0)	1.00
*Missing**	*2*	*2*	
AST at enrollment (IU/L)			
≤ Grade 2	162 (100.0)	70 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*2*	*0*	
AST at 6-12 weeks postpartum (IU/L)			
≤ Grade 2	161 (99.4)	68 (100.0)	
Grade 3/4	1 (0.6)	0 (0.0)	1.00
*Missing**	*2*	*2*	
Total bilirubin at enrollment (mg/dL)			
≤ Grade 2	160 (100.0)	70 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*4*	*0*	
Total bilirubin at 6-12 weeks postpartum (mg/dL)			
≤ Grade 2	161 (100.0)	67 (98.5)	
Grade 3/4	0 (0.0)	1 (1.5)	0.30
*Missing**	*3*	*2*	
Cholesterol at enrollment (mg/dL)			
≤ Grade 2	158 (97.5)	64 (91.4)	
Grade 3/4	4 (2.5)	6 (8.6)	0.07
*Missing**	*2*	*0*	
Cholesterol at 6-12 weeks postpartum (mg/dL)			
≤ Grade 2	157 (96.9)	68 (100.0)	
Grade 3/4	5 (3.1)	0 (0.0)	0.32
*Missing**	*2*	*2*	
Triglycerides at enrollment (mg/dL)			
≤ Grade 2	161 (99.4)	70 (100.0)	
Grade 3/4	1 (0.6)	0 (0.0)	1.00
*Missing**	*2*	*0*	

(Cont.)

Table 1. Maternal categorical variables by LPV/r dosing group

Characteristic	Standard dosing (Group 1) n = 164 (%)	Increased dosing (Group 2) n = 70 (%)	p-value
Triglycerides at 6-12 weeks postpartum (mg/dL)			
≤ Grade 2	162 (100.0)	68 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*2*	*2*	

p-values calculated using Fisher's exact test; * missing data; NC, not calculated.

Table 2. Maternal continuous variables by LPV/r dosing group

Characteristic	Standard dosing (Group 1) Mean (SD)	Increased dosing (Group 2) Mean (SD)	p-value
Age at delivery (years)	29.6 (5.5)	27.1 (6.4)	0.004
CD4 count at enrollment (cells/mm^3)	486.1 (292.7)	535.4 (303.9)	0.24
CD4 count at hospital discharge (cells/mm^3)	559.6 (292.0)	605.8 (307.5)	0.29
Log HIV RNA at enrollment (copies/mL)	2.6 (1.0)	3.0 (0.7)	0.007
Log HIV RNA at hospital discharge (copies/mL)	2.3 (0.8)	2.8 (0.7)	0.0002
ALT at enrollment (IU/L)	15.8 (14.9)	14.1 (11)	0.34
ALT at 6-12 weeks postpartum (IU/L)	24.1 (22.7)	17.2 (9.0)	0.001
AST at enrollment (IU/L)	21.5 (19.4)	19.6 (9.5)	0.32
AST at 6-12 weeks postpartum (IU/L)	26.4 (33.6)	19.9 (6.5)	0.02
Total bilirubin at enrollment (mg/dL)	0.5 (0.3)	0.5 (0.3)	0.63
Total bilirubin at 6-12 weeks postpartum (mg/dL)	0.5 (0.3)	0.6 (0.6)	0.72
Cholesterol at enrollment (mg/dL)	204.5 (42.1)	220.4 (53.2)	0.03
Cholesterol at 6-12 weeks postpartum (mg/dL)	186.8 (46.3)	178.6 (37.1)	0.15
Triglycerides at enrollment (mg/dL)	231.6 (106.4)	235.4 (93)	0.80
Triglycerides at 6-12 weeks postpartum (mg/dL)	152.6 (77.7)	125.5 (63.5)	0.01

p-values calculated using Student's *t* test for comparison of means.

mean plasma viral load was significantly higher in Group 2 at enrollment (p = 0.007) and at the hospital discharge (p = 0.0002) (Table 2), there were no statistically significant differences in the percentages of subjects with viral loads ≥ 1,000 copies/mL at enrollment or at hospital discharge. Similarly, the percentage of subjects whose plasma viral load decreased from enrollment to hospital discharge was not different between groups (Table 1).

At enrollment, women in Group 2 had higher mean cholesterol values (p = 0.03). At 6-12 weeks postpartum, women in Group 1 had higher mean alanine aminotransferase (ALT) (p = 0.001), aspartate aminotransferase (AST) (p = 0.02), and triglyceride (p = 0.01) values (Table 2). The overall proportion of women with Grade 3 or 4 adverse events was very low (≤ 1.5%, except cholesterol 8.6%), and there were no statistically significant differences between the proportions of women in each group with Grade 3 or 4 adverse events related to ALT, AST, total bilirubin, cholesterol, or triglycerides (Table 1).

Infant variables are shown in Tables 3 and 4. There were no statistically significant differences in gestational age, birth weight, gender, or HIV infection status according to standard versus increased dose of LPV/r (Table 3). As shown in Table 4, infants born to mothers in Group 1 had significantly higher mean ALT values at birth (p = 0.0006), and creatinine values at birth and at 6-12 weeks (p < 0.0001). The overall proportion of infants with Grade 3 or 4 adverse events was very low (≤ 1.9%), and there were no statistically significant differences in the proportions of infants in each group with Grade 3 or 4 adverse events related to ALT, AST, blood urea nitrogen (BUN), or creatinine (Table 3).

Table 3. Infant categorical variables by maternal LPV/r dosing group

Characteristic	Standard dosing (Group 1) n = 164 (%)	Increased dosing (Group 2) n = 70 (%)	p-value
Gestational age at birth (completed weeks)			
<37	16 (9.8)	6 (8.7)	
≥37	147 (90.2)	63 (91.3)	1.00
*Missing**	*1*	*1*	
Birth weight (grams)			
<2,500	33 (20.2)	11 (15.9)	
≥2,500	130 (79.8)	58 (84.1)	0.58
*Missing**	*1*	*1*	
Gender			
Female	77 (47.2)	32 (46.4)	
Male	86 (52.8)	37 (53.6)	1.00
*Missing**	*1*	*1*	
HIV infection status			
Infected	1 (0.6)	0 (0.0)	
Uninfected	129 (79.6)	56 (81.2)	1.00
Indeterminate	32 (19.8)	13 (18.8)	
*Missing**	*2*	*1*	
ALT at birth (IU/L)			
≤ Grade 2	158 (100.0)	63 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*6*	*7*	
ALT at 6-12 weeks of age (IU/L)			
≤ Grade 2	159 (98.8)	63 (98.4)	
Grade 3/4	2 (1.2)	1 (1.6)	1.00
*Missing**	*3*	*6*	
AST at birth (IU/L)			
≤ Grade 2	155 (98.1)	61 (98.4)	
Grade 3/4	3 (1.9)	1 (1.6)	1.00
*Missing**	*6*	*8*	
AST at 6-12 weeks of age (IU/L)			
≤ Grade 2	160 (99.4)	64 (100.0)	
Grade 3/4	1 (0.6)	0 (0.0)	1.00
*Missing**	*3*	*6*	
BUN at birth (mg/dL)			
≤ Grade 2	124 (100.0)	61 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*40*	*9*	
BUN at 6-12 weeks of age (mg/dL)			
≤ Grade 2	125 (98.4)	62 (100.0)	
Grade 3/4	2 (1.6)	0 (0.0)	1.00
*Missing**	*37*	*8*	
Creatinine at birth (mg/dL)			
≤ Grade 2	125 (100.0)	60 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*39*	*10*	

(Cont.)

Table 3. Infant categorical variables by maternal LPV/r dosing group

Characteristic	Standard dosing (Group 1) n = 164 (%)	Increased dosing (Group 2) n = 70 (%)	p-value
Creatinine at 6-12 weeks of age (mg/dL)			
≤ Grade 2	127 (100.0)	62 (100.0)	
Grade 3/4	0 (0.0)	0 (0.0)	NC
*Missing**	*37*	*8*	

p-values calculated using Fisher's exact test; * missing data; NC, not calculated.

Table 4. Infant continuous variables by LPV/r dosing group

Characteristic	Standard dosing (Group 1) Mean (SD)	Increased dosing (Group 2) Mean (SD)	p-value
ALT at birth (IU/L)	19.0 (9.4)	15.4 (5.9)	0.0006
ALT at 6-12 weeks of age (IU/L)	35.8 (35.9)	28.6 (33.5)	0.16
AST at birth (IU/L)	65.0 (36.5)	59.1 (29.4)	0.26
AST at 6-12 weeks of age (IU/L)	43.5 (26.6)	40.3 (22.9)	0.40
BUN at birth (mg/dL)	9.3 (6.6)	9.7 (7.0)	0.76
BUN at 6-12 weeks of age (mg/dL)	13.3 (9.3)	14.7 (9.8)	0.33
Creatinine at birth (mg/dL)	0.7 (0.2)	0.5 (0.2)	< 0.0001
Creatinine at 6-12 weeks of age (mg/dL)	0.4 (0.1)	0.3 (0.1)	< 0.0001

p-values calculated using Student's *t* test for comparison of means.

DISCUSSION

Since most studies of LPV/r have been performed in resource-rich settings, among ARV-naïve, non-pregnant adults or ARV-experienced subjects, extrapolation to other populations may be limited by differences in genetics, diet, concomitant comorbidities, and other factors. For this reason, we undertook this analysis of laboratory adverse events among HIV-infected pregnant women and their infants in Brazil according to LPV/r dosing during the third trimester of pregnancy. In this analysis, most women (70.1%) used standard LPV/r dosing during the third trimester of pregnancy and the median duration of use of either standard or increased dosing of LPV/r was over two months. Women in the standard dosing group were more likely to have more advanced clinical disease and to have used ARVs for treatment. They were less likely to have CD4 counts of 500 cells/mm^3 or more. The mean plasma viral load was higher in the increased dosing group. Although there were statistically significant differences between groups in terms of mean AST, ALT, cholesterol, and triglyceride values, none of these differences were clinically meaningful. The overall proportion of women with Grade 3 or 4 adverse events was very low, and there were no statistically significant differences in the proportions of women in each group with severe adverse events related to ALT, AST, total bilirubin, cholesterol, or triglycerides. Although there were statistically significant differences between infant groups in terms of ALT and creatinine values, none of these differences were clinically meaningful. The overall proportion of infants with Grade 3 or 4 adverse events was very low, and there were no statistically significant differences in the proportions of infants in each group with severe adverse events related to ALT, AST, BUN, or creatinine.

Lipid abnormalities and elevations in liver enzyme concentrations have been associated with use of LPV/r. Like other PIs, LPV/r may cause significant lipid elevations and fat redistribution. Hypertriglyceridemia and hypercholesterolemia were the most frequently observed laboratory abnormalities in LPV/r recipients in clinical trials and may be the reason for discontinuation of therapy in some HAART-experienced patients.[18] Increases in total cholesterol and

triglycerides are seen within the first month of starting therapy and are relatively stable after this time.[19] Total Grade 3 and 4 cholesterol and triglyceride elevations appear to occur more frequently in PI-experienced than in PI-naive LPV/r-treated patients. Some trials have found that the lipid derangements caused by LPV/r were more severe than those caused by other PIs such as atazanavir, atazanavir/ritonavir, or nelfinavir,[20,21] but other trials reported similar elevations in triglycerides and cholesterol in LPV/r recipients as compared to subjects receiving other PIs.[22] PIs including LPV/r have been associated with insulin resistance, new onset diabetes, and worsening of preexisting diabetes requiring hypoglycemic agents in some patients. LPV/r can cause transient elevations in transaminase levels, but these are usually not clinically meaningful. The incidence of severe hepatic events in patients receiving LPV/r is very low. Hepatitis C coinfection and baseline elevations in transaminases may be associated with severe liver events in LPV/r recipients.[23] Robbins *et al.*[24] published data showing that doses of LPV/r higher than those currently approved by the FDA are safe and well tolerated for up to 48 weeks in children and adolescents with HIV infection. There was no significant increase in plasma triglycerides, and while there was an initial statistically significant increase in cholesterol, this was of modest size and did not worsen over the course of the study. There was no evidence of hepatic or cardiac toxicity with these higher doses.

A French study explored whether LPV/r exposure during pregnancy was associated with adverse outcomes.[25] For each HIV-infected woman, two uninfected women matched by age, parity and geographical origin were selected among patients delivering during the same period. Rates of placental complications and gestational glucose intolerance were not higher among HIV-infected women than in controls. However, the rate of preterm birth was higher among HIV-infected women (21%) than among controls (10%) ($p < 0.01$).

One of the strengths of our study is that it is a large multicenter cohort that includes prospectively collected data. Women and children were enrolled and followed at the same health care facility at each site, where they received primary HIV and other medical care, and it is unlikely that any important clinical and laboratory events were missed among those retained in care. The observational study design is a limitation, in that women were prescribed LPV/r standard dose *vs*. higher dose by their physicians (and not by randomization). In addition, the women enrolled in Group 1 on average were older, more likely to be using ARVs for treatment (rather than prophylaxis), and appeared to have more advanced HIV disease (more women at CDC clinical disease stage B/C at both enrollment and hospital discharge) than women in Group 2. However, given the low adverse event rates for both mothers and infants in the entire study population, these baseline differences between the two dose groups are unlikely to affect the main findings of our analysis. Finally, adherence data were not collected as part of the Perinatal Protocol (2002-2007, but were during the LILAC Protocol (2008-current).

In summary, in this population of HIV-infected women and their infants in Brazil, the proportions of subjects with severe laboratory adverse events were very low. These results suggest that increased LPV/r dosing during the third trimester of pregnancy is safe for both HIV-infected women and their infants. Further assessments of LPV/r dosing during pregnancy and maternal/infant adverse events are warranted.

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