Postpartum changes in plasma viral load and CD4 percentage among HIV-infected women from Latin American and Caribbean countries: the NISDI Perinatal Study

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The goal of this study was to evaluate changes in plasma human immunodeficiency virus (HIV) RNA concentration [viral load (VL)] and CD4$^+$ percentage (CD4%) during 6-12 weeks postpartum (PP) among HIV-infected women and to assess differences according to the reason for receipt of antiretrovirals (ARVs) during pregnancy [prophylaxis (PR) vs. treatment (TR)]. Data from a prospective cohort of HIV-infected pregnant women (National Institute of Child Health and Human Development International Site Development Initiative Perinatal Study) were analyzed. Women experiencing their first pregnancy who received ARVs for PR (started during pregnancy, stopped PP) or for TR (initiated prior to pregnancy and/or continued PP) were included and were followed PP. Increases in plasma VL (≥ 0.5 $\log_{10}$) and decreases in CD4% ($\geq$ 20% relative decrease in CD4%) between hospital discharge (HD) and PP were assessed. Of the 1,229 women enrolled, 1,119 met the inclusion criteria (PR: 601; TR: 518). At enrollment, 87% were asymptomatic. The median CD4% values were: HD [34% (PR); 25% (TR)] and PP [29% (PR); 24% (TR)]. The VL increases were 60% (PR) and 19% (TR) ($p < 0.0001$). The CD4% decreases were 36% (PR) and 18% (TR) ($p < 0.0001$). Women receiving PR were more likely to exhibit an increase in VL [adjusted odds ratio (AOR) 7.7 (95% CI: 5.5-10.9) and a CD4% decrease (AOR 2.3; 95% CI: 1.6-3.2). Women receiving PR are more likely to have VL increases and CD4% decreases compared to those receiving TR. The clinical implications of these VL and CD4% changes remain to be explored.

Key words: HIV - pregnancy - postpartum period - viral load - CD4 counts

Women infected with human immunodeficiency virus type 1 (HIV) receive antiretrovirals (ARVs) during pregnancy for prophylaxis (PR) [prevention of mother-to-child transmission (MTCT) of HIV] or for the treatment (TR) of their own HIV infection. Concerns have been raised regarding the discontinuation of ARVs after delivery (among women who received ARVs for PR) in light of the results of the studies of structured TR interruption among HIV-infected individuals receiving ARVs for TR (Ananworanich et al. 2006, El-Sadr et al. 2006, Ruiz et al. 2007). For example, in the SMART trial, HIV-infected subjects with CD4$^+$ counts above 350 cells/mm^3 were randomly assigned to the continuous or episodic receipt of ARV therapy. The latter group only used ARVs when the CD4$^+$ count decreased to below 250 cells/mm^3 and had a significantly higher rate of opportunistic infections and all-cause mortality (El-Sadr et al. 2006). The results of studies evaluating changes in the plasma HIV RNA concentration [viral load (VL)], the CD4$^+$ lymphocyte percentage (CD4%) or absolute CD4$^+$ lymphocyte count, or the HIV clinical disease stage in the postpartum (PP) period among HIV-infected women continuing or discontinuing ARVs after pregnancy have shown conflicting results (Cao et al. 1997, Melvin et al. 1997, Watts et al. 2003, Martin et al. 2006, Tungsiripat et al. 2007, Cavallo et al. 2010). To avoid the effect of a higher volume of distribution on absolute CD4$^+$ lymphocyte counts, the CD4% should be used for monitoring T lymphocytes during pregnancy and PP (Miotti et al. 1992, Ekouevi et al. 2007). We analyzed data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal Study to determine factors associated with a VL increase or a CD4% decrease among HIV-infected women who received ARVs during pregnancy, according to whether or not ARVs were discontinued after delivery.

PATIENTS, MATERIALS AND METHODS

NISDI Perinatal Study - The NISDI Perinatal Study was a prospective cohort study of HIV-infected women and their children conducted at multiple sites in Latin

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America and in the Caribbean (Read et al. 2007). ARVs for HIV-infected women and children had to be available at each participating site, along with alternatives to breastfeeding. The primary objectives of this observational study included assessing the use of ARVs for the prevention of MTCT and for the woman's own health. Enrollment began in 2002 and was completed in 2007. Women were eligible for enrollment if their pregnancy was confirmed, their HIV infection documented, they intended to deliver at a participating clinical site and to be followed up (along with their children) after delivery or birth and they were willing and able to provide informed consent. Enrollment had to occur before delivery. Signed informed consent was obtained for all subjects before enrollment into the study. The protocol was approved by the ethical review board at each clinical site, as well as by institutional review boards at the sponsoring institution (NICHD) and at the data management center (Westat).

Maternal study visits were conducted during pregnancy, at delivery, at hospital discharge (HD) after delivery and at 6-12 weeks and six months PP. During each of these visits, a medical history was obtained, a physical examination was performed and laboratory samples were obtained (except at the delivery and the 6-month PP visits). The virological, immunological and clinical characteristics of the women were assessed during pregnancy, at the time of HD after delivery and at the 6-12 week PP visit. Maternal clinical disease staging was performed at each visit using the US Centers for Disease Control and Prevention classification system (CDC 1992).

Study population and definitions for this analysis - The study population for this analysis was restricted to women enrolled in the NISDI Perinatal Study as of October 2007, with their first pregnancy during the study, who were followed until at least the 6-12 week PP visit, who received ARVs during pregnancy and for whom the reason for receipt ARVs was known. The receipt of ARVs during pregnancy was categorized as either PR or TR. Women were classified as having received PR if they were not receiving ARVs when they became pregnant, but they initiated one or more ARVs during pregnancy and discontinued these drugs at or before the 6-12 week PP visit. Otherwise, women were classified as having received TR if they were receiving ARVs when they became pregnant or continued ARVs after the 6-12 week PP visit. The outcome variables of interest were changes between the HD visit and the 6-12 week PP visit defined as: an increase in plasma VL (≥ 0.5 $\log_{10}$ increase) and a decline in CD4% ($\geq 20\%$ relative decrease). Other covariates were defined as follows: homemakers, unemployed individuals and students were classified as not gainfully employed outside of the home and all others were classified as gainfully employed outside of the home. A maternal history of substance use during the index pregnancy was ascertained through maternal interview at enrollment.

Data collected from a small part of the current cohort (4% of the study population) has been published elsewhere (Cavallo et al. 2010).

Statistical analysis - The associations of categorical variables with VL increase and CD4% decline at the 6-12 week visit were evaluated using the Fisher-Freeman-Halton exact test. Variables at least marginally associated with VL increase and CD4% decline ($p \leq 0.20$) were considered candidates for multivariable logistic regression modelling. Both stepwise selection and backward elimination strategies were applied to determine whether both selection procedures arrived at the same parsimonious model (using a 5% significance level).

Ethics - The ethical protocol was approved by the ethical review board at each clinical site, as well as by institutional review boards at the sponsoring institution (NICHD) and at the data management center (Westat).

RESULTS

Size and characteristics of the study population - As of October 2007, there were 1,229 women enrolled in the NISDI Perinatal Study. Of these, there were 1,174 first pregnancies in the study. Of the 1,174 pregnant women, three were lost to follow-up between enrollment and the 6-12 week visit. Of the remaining 1,171 women, 1,163 received one or more ARVs during pregnancy. The reason for the receipt of ARVs during pregnancy could not be determined for 44 women. Thus, the study population comprised 1,119 women (601 received ARVs as PR and 518 received ARVs as TR).

The characteristics of the study population of 1,119 women, overall and according to the receipt of ARVs for PR or TR, are shown in Table I. Several characteristics varied significantly ($p < 0.05$) according to the receipt of PR vs. TR, including country of residence, age, education and tobacco use during pregnancy.

At enrollment and at HD, a greater proportion of women in the PR group were asymptomatic or only mildly symptomatic (clinical stage A) than women in the TR group. Women in the PR group were more likely to have received 1-2 nucleoside reverse transcriptase inhibitors (NRTIs) as their most complex ARV regimen of $\geq$ 28 days during pregnancy or to have received ARVs for < 28 days during pregnancy, than women in the TR group. Finally, at 6-12 weeks PP, women in the PR group were more likely to be at clinical stage A than women in the TR group (Table I).

A greater proportion of women in the PR group had a CD4% $\geq$ 29% at enrollment (63.6%) and at HD (74.2%). At 6-12 weeks PP, they were more likely to have a CD4% $\geq$ 29% (52.7%) than women in the TR group. The percentage of women with VL < 1,000 copies/mL at enrollment and at HD was not different between the two groups. However, women in the TR group were more likely to have a VL < 1,000 copies/mL at 6-12 weeks PP (67.4%; $p < 0.0001$) (Table II).

The median CD4% at HD was 35% (range 6-67%) in the PR group and 26% (1-62%) in the TR group. At 6-12 weeks PP, the median CD4% was 30% (3-69%) in the PR group and 25% (1-53%) in the TR group. The median VL at HD was 200 copies/mL for both groups. However, at 6-12 weeks PP, the median VL was 200 copies/mL for the TR group, compared to 7,910 copies/mL for the PR group.

TABLE I

Characteristics of the study population, overall and according to reason for receipt of antiretrovirals (ARV) during pregnancy

	Prophylaxis (n = 601) n (%)	Treatment (n = 518) n (%)	Total (n = 1,119) n (%)	p value
At enrollment				
Country of residence				
Argentina	145 (24.1)	192 (37.1)	337 (30.1)	< 0.0001
Bahamas	27 (4.5)	14 (2.7)	41 (3.7)	-
Brazil	379 (63.1)	261 (50.4)	640 (57.2)	-
Jamaica	26 (4.3)	7 (1.4)	33 (3)	-
Mexico	13 (2.2)	29 (5.6)	42 (3.8)	-
Peru	11 (1.8)	15 (2.9)	26 (2.3)	-
Age (years)				
< 20	49 (8.2)	15 (2.9)	64 (5.7)	< 0.0001
20-29	373 (62.1)	245 (47.3)	618 (55.2)	-
≥ 29	179 (29.8)	258 (49.8)	437 (39)	-
Education (years)				
≥ 13	20 (3.3)	35 (6.8)	55 (4.9)	0.0008
7-12	363 (60.4)	340 (65.6)	703 (62.8)	-
0-6	218 (36.3)	143 (27.6)	361 (32.3)	-
Crowding (number of persons living in the household)				
1-3	260 (43.3)	245 (47.3)	505 (45.1)	0.18
≥ 4	341 (56.7)	273 (52.7)	614 (54.9)	-
Gainfully employed outside the home				
Yes	134 (22.3)	126 (24.3)	260 (23.2)	0.42
No	467 (77.7)	392 (75.7)	859 (76.8)	-
Tobacco use during pregnancy				
Yes	159 (26.5)	108 (20.8)	267 (23.9)	0.03
No	442 (73.5)	410 (79.2)	852 (76.1)	-
Alcohol use during pregnancy				
Yes	57 (9.5)	47 (9.1)	104 (9.3)	0.81
No	544 (90.5)	471 (90.9)	1,015 (90.7)	-
Cocaine use during pregnancy				
Yes	18 (3)	12 (2.3)	30 (2.7)	0.48
No	583 (97)	506 (97.7)	1,089 (97.3)	-
Marijuana use during pregnancy				
Yes	12 (2)	13 (2.5)	25 (2.2)	0.56
No	589 (98)	505 (97.5)	1,094 (97.8)	-
Clinical disease stage				
A	578 (96.2)	395 (76.2)	973 (87)	< 0.0001
B	13 (2.2)	46 (8.9)	59 (5.3)	-
C	10 (1.7)	77 (14.9)	87 (7.8)	-
At hospital discharge following delivery				
Clinical disease stage				
A	576 (95.8)	392 (75.7)	968 (86.5)	< 0.0001
B	14 (2.3)	48 (9.3)	62 (5.5)	-
C	11 (1.8)	78 (15.1)	89 (8)	-
Most complex ARV regimen of ≥ 28 days during pregnancy				
2 NRTIs + 1 PI	324 (53.9)	259 (50)	583 (52.1)	< 0.0001
2 NRTIs + 1 NRTI	138 (23)	215 (41.5)	353 (31.5)	-
1-2 NRTIs	98 (16.3)	16 (3.1)	114 (10.2)	-
ARVs < 28 days	36 (6)	16 (3.1)	52 (4.6)	-
Other	5 (0.8)	12 (2.3)	17 (1.5)	-
At 6-12 weeks postpartum				
Clinical disease stage				
A	575 (95.7)	389 (75.1)	964 (86.2)	< 0.0001
B	15 (2.5)	50 (9.6)	65 (5.8)	-
C	11 (1.8)	79 (15.2)	90 (8)	-

NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

TABLE II
Results of CD4% and viral load (VL) according to reason for receipt of antiretrovirals during pregnancy

	Prophylaxis (n = 601) n (%)	Treatment (n = 518) n (%)	Total (n = 1,119)	p value
	At enrollment			
CD4%				
< 14	14 (2.5)	78 (16.5)	92 (9)	< 0.0001
14-28	187 (33.8)	255 (53.8)	442 (43)	-
≥ 29	352 (63.6)	141 (29.8)	493 (48)	-
Unknown	48	44	-	-
VL (copies/mL)				
< 1,000	357 (60.7)	292 (56.8)	649 (58.9)	0.35
1,000 ≤ 10,000	120 (20.4)	109 (21.2)	229 (20.8)	-
≥ 10,000	111 (18.9)	113 (22)	224 (20.3)	-
Unknown	13	4	-	-
	At hospital discharge following delivery			
CD4%				
< 14	7 (1.4)	57 (12.3)	64 (6.7)	< 0.0001
14-28	122 (24.4)	231 (50)	353 (36.7)	-
≥ 29	370 (74.2)	174 (37.7)	544 (56.6)	-
Unknown	102	56	-	-
VL (copies/mL)				
< 1,000	450 (84.9)	400 (80.6)	850 (82.8)	0.10
1,000 ≤ 10,000	44 (8.3)	61 (12.3)	105 (10.2)	-
≥ 10,000	36 (6.8)	35 (7.1)	71 (6.9)	-
Unknown	71	22	-	-
	At 6-12 weeks postpartum			
CD4%				
< 14	19 (3.3)	55 (11.3)	74 (7)	< 0.0001
14-28	253 (44)	260 (53.4)	513 (48.3)	-
≥ 29	303 (52.7)	172 (35.3)	475 (44.7)	-
Unknown	26	31	-	
VL (copies/mL)				
< 1,000	142 (24)	347 (67.4)	489 (44.2)	< 0.0001
1,000 ≤ 10,000	181 (30.6)	74 (14.4)	255 (23.1)	-
≥ 10,000	268 (45.4)	94 (18.2)	362 (32.7)	-
Unknown	10	3	-	-

CD4%: $CD4^+$ lymphocyte percentage.

VL increase and CD4% decline - Univariate analyses assessing associations with an increase in VL between HD and the 6-12 week PP visit were performed. Several factors were marginally associated ($p \leq 0.20$) with a VL increase and were included in logistic regression analyses, including the receipt of ARVs for PR ($p < 0.0001$), the country of residence ($p < 0.0001$), age (years) ($p = 0.004$), education (years) ($p = 0.03$) and alcohol ($p = 0.12$) and cocaine use ($p = 0.08$) during pregnancy. Other variables associated with a VL increase were CD4% ($p < 0.0001$), VL (copies/mL) ($p < 0.0001$) and HIV clinical disease stage ($p < 0.0001$) before the 6-12 week PP visit. Specifically, those with lower CD4% (at enrollment and at HD) were less likely to have a VL increase. Those with higher VL values (at enrollment and at HD) were less likely to have a VL increase. Finally, those with a more advanced HIV clinical disease stage (at enrollment and at HD) were less likely to have a VL increase. Multivariable modelling incorporating all of the above variables resulted in a final model including four variables (Table III): reason for the receipt of ARVs during pregnancy, the country of residence, VL at HD and clinical disease stage at HD. The country of residence was retained in the model to control for site variability. Those who received ARV PR during pregnancy had an almost eight-fold increase in risk of a VL increase at 6-12 weeks

TABLE III

Risk of viral load (VL) increase [unadjusted (OR) and adjusted odds ratios (AOR)]

		VL increase (n = 406) n (%)	No VL increase (n = 609) n (%)	p value[a]	OR	95% CI	AOR	95% CI
Reason for receipt of antiretrovirals during pregnancy	Prophylaxis	313 (60)	209 (40)	< 0.0001	6.4	4.8-8.6	7.7	5.5-10.9
	Treatment	93 (18.9)	400 (81.1)	-	1	-	-	-
Country of residence (at enrollment)	Argentina	149 (46.3)	173 (53.7)	< 0.0001	1.4	1.1-1.9	2.1	1.5-3.1
	Bahamas	18 (56.2)	14 (43.8)	-	2.2	1.1-4.6	2.4	0.9-6.0
	Brazil	212 (37.2)	358 (62.8)	-	1	-	1	-
	Jamaica	16 (61.5)	10 (38.5)	-	2.7	1.2-6.1	1.6	0.6-4.4
	Mexico	8 (20)	32 (80)	-	0.4	0.2-0.9	1.3	0.5-3.3
	Peru	3 (12)	22 (88)	-	0.2	0.1-0.8	0.3	0.1-1.1
VL (copies/mL) at hospital discharge	< 1,000	400 (47.6)	441 (52.4)	< 0.0001	1	-	1	-
	≥ 1,000	6 (3.4)	168 (96.6)	-	0.04	0.02-0.09	0.03	0.01-0.08
Clinical disease stage at hospital discharge	A	384 (44.1)	487 (55.9)	< 0.0001	1	-	1	-
	B	15 (24.2)	47 (75.8)	-	0.4	0.2-0.7	0.9	0.4-1.7
	C	7 (8.5)	75 (91.5)	-	0.1	0.05-0.3	0.3	0.1-0.7

a: p value for unadjusted OR using Fisher-Freeman-Halton exact test for assessment of association of each characteristic with the outcome; CI: confidence interval.

PP compared to those who received ARVs for TR [adjusted odds ratio (AOR) = 7.7; 95% CI 5.5-10.9]. Women with VLs ≥ 1,000 copies/mL at HD were significantly less likely to experience a VL increase at 6-12 weeks compared to those with VL < 1,000 copies/mL. Finally, women with more advanced clinical HIV disease at HD were significantly less likely to have a VL increase that those who were asymptomatic (Table III).

Univariate analyses assessing associations with CD4% decline between HD and the 6-12 week PP visit also were performed. Variables marginally associated ($p \leq 0.20$) with a CD4% decline that were incorporated into logistic regression analyses included crowding (number of persons living in the household) ($p = 0.11$), alcohol ($p = 0.12$) and marijuana ($p = 0.12$) use during pregnancy and the receipt of ARVs during pregnancy for PR ($p < 0.0001$). Those with CD4% < 14% at enrollment ($p = 0.04$) and at HD ($p < 0.0001$) were less likely to have a CD4% decline. Similarly, those with more advanced HIV clinical disease at enrollment ($p = 0.0046$) and at HD ($p = 0.0049$) were less likely to have a CD4% decline. Multivariable modelling incorporating all of the above variables resulted in a final model including reason for the receipt of ARVs during pregnancy, country of residence and CD4% at HD (Table IV). As before, country of residence was retained in the model to control for site variability. Those who received ARV PR during pregnancy had a higher risk of a CD4% decline at 6-12 weeks PP compared to those who received ARVs for TR (AOR = 2.3; 95% CI 1.6-3.2). Those with a CD4% of 14-28% at HD were less likely to have a CD4% decline at 6-12 weeks PP compared to those with a CD4% ≥ 29% [AOR = 0.60 (95% CI 0.4-0.8)] (Table IV).

DISCUSSION

In this study of a relatively healthy population of HIV-infected women [at enrollment, approximately half had a CD4% ≥ 29%, almost 60% had a VL below 1,000 copies/mL and approximately 87% were asymptomatic (clinical stage A)], there was little clinical progression over time (by 6-12 weeks PP, 86% of women remained at clinical stage A). Although there were changes in CD4% and VL values over time (60% of women who received ARVs during pregnancy for PR had a VL increase and 40% had a CD4% decline during the first few weeks PP vs. 19% and 18%, respectively, of women who received ARVs during pregnancy for TR), most women who received ARVs for PR maintained a CD4% ≥ 29% (74% at HD and 53% at 6-12 weeks PP). Eighty-five percent of women who received ARVs for PR during pregnancy had a VL < 1,000 copies/mL at HD. However, only 24% of these women had a VL < 1,000 copies/mL at 6-12 weeks PP.

The interruption of ARV PR after delivery is not completely analogous to structured ARV interruption (Ananworanich et al. 2006, Danel et al. 2006, El-Sadr et al. 2006, Pai et al. 2006, Ruiz et al. 2007). With the use of ARVs for the prevention of the MTCT of HIV, assuming the woman does not meet criteria for ARV TR, maternal ARVs are discontinued after the delivery of the infant. With the interruption of ARV TR, structured according to VL and $CD4^+$ count results, patients whose immunological status suggests a low risk of disease progression either continued therapy or interrupted it until the $CD4^+$ count reached a certain threshold. Studies generally have demonstrated worse outcomes for those with structured TR interruptions.

TABLE IV

Risk of $CD4^+$ lymphocyte percentage (CD4%) decline [unadjusted (OR) and adjusted odds ratios (AOR)]

		CD4% decline (n = 256) n (%)	CD4% decline (n = 692) n (%)	p value[a]	OR	95% CI	AOR	95% CI
Reason for receipt of antiretrovirals during pregnancy	Prophylaxis	176 (35.7)	317 (64.3)	< 0.0001	2.6	1.9-3.5	2.3	1.6-3.2
	Treatment	80 (17.6)	375 (82.4)	-	-	1	1	-
Country of residence	Argentina	89 (28.4)	224 (71.6)	0.60	1.0	0.8-1.4	1.2	0.9-1.7
	Bahamas	11 (28.2)	28 (71.8)	-	1.0	0.5-2.2	1.0	0.5-2.0
	Brazil	139 (27.4)	369 (72.6)	-	-	1	1	-
	Jamaica	3 (12.5)	21 (87.5)	-	0.4	0.1-1.3	0.3	0.1-1.1
	Mexico	9 (23.1)	30 (76.9)	-	0.8	0.4-1.7	1.1	0.5-2.6
	Peru	5 (20)	20 (80)	-	0.7	0.2-1.8	0.8	0.3-2.3
CD4% at hospital discharge	< 14	10 (15.6)	54 (84.4)	< 0.0001	0.4	0.2-0.7	0.6	0.3-1.2
	14-28	67 (19.3)	280 (80.7)	-	0.5	0.4-0.7	0.6	0.4-0.8
	≥ 29	179 (33.3)	358 (66.7)	-	-	1	1	-

a: p value for unadjusted OR using Fisher-Freeman-Halton exact test for assessment of association of each characteristic with the outcome; CI: confidence interval.

Previous studies have evaluated changes in the absolute $CD4^+$ count (Read et al. 2007) or percentage (Watts et al. 2003) among HIV-infected women who did or did not discontinue ARVs after delivery. As noted previously, the CD4% should be used to monitor T lymphocytes during pregnancy and PP (Miotti et al. 1992, Ekouevi et al. 2007). In a secondary analysis of the PACTG 185 clinical trial database (Watts et al. 2003), women who continued ARV therapy after delivery were compared to those who discontinued therapy. All enrolled women had $CD4^+$ lymphocyte counts below 500 cells/mm^3 at enrollment. Most (86%) received zidovudine (ZDV) alone, while 14% received two NRTIs during pregnancy. Changes in $CD4^+$ percentages between delivery and 18 months PP did not differ significantly according to whether ZDV monotherapy was continued or discontinued following delivery.

Similarly, other studies have assessed VL changes among HIV-infected women according to the continuation or discontinuation of ARVs after delivery (Cao et al. 1997, Melvin et al. 1997, Watts et al. 2003, Martin et al. 2006, Tungsiripat et al. 2007). Some studies have suggested no change in VL PP, although others indicated VL increases. First, in a retrospective study of HIV-infected women who discontinued ARVs at delivery (Tungsiripat et al. 2007), median VLs at 12-96 weeks PP were similar to values obtained during pregnancy. In another study of 44 HIV-infected pregnant women, 23 women initiated ZDV therapy during pregnancy, 17 women did not use ARVs and four women used ZDV before and during pregnancy (Melvin et al. 1997). Overall, VLs remained stable until six weeks PP, but there was a trend toward an increase in VL values PP among those women who received ZDV therapy only during pregnancy. However, in the Ariel Project (Cao et al. 1997), in which most women (85%) used ZDV during pregnancy for the prevention of MTCT and only a minority of women received it before pregnancy and continued after delivery (TR), a significant VL increase was noted at two and six months PP. Among women enrolled in the PACTG 185 clinical trial (Watts et al. 2003), increases in VLs from delivery to 12 weeks PP were observed, but VL changes were similar among women continuing or discontinuing therapy after delivery. In a study of HIV-infected pregnant women who received ZDV alone, combination ARV therapy and combination ARV PR (Martin et al. 2006), follow-up continued for an average of 33 months after delivery. At the end of follow-up, the median VL was higher in the ARV PR group (3.5 log copies/mL) compared to the TR group (1.7 log copies/mL). However, at the last follow-up, the proportion of women on combination ARV therapy with VLs < 50 copies/mL did not differ significantly according to whether ARV TR or PR was used during pregnancy (78% and 79%, respectively).

Finally, in a recent study comprising 112 HIV-infected pregnant women treated with potent ARVs (60 taking ARV for PR and 52 for TR), VL rebound affected women much more often in the PR than in the TR group (84.7% vs. 15.3%; $p < 0.001$) six months after delivery and was associated with ARV discontinuation. In addition, there was a higher decline in CD4 cell percentage among women in the PR group at this time (Cavallo et al. 2010).

We believe that these apparently conflicting results in the literature regarding the interruption of ARVs after delivery and VL rebound and/or CD4% decline may be related to the increased activity of the current ARV combinations against HIV, which are predominantly triple regimens, offered to most of our pregnant women, in comparison to mono or dual therapy, which were used by women in older studies and were not as efficient at reducing VL and improving CD4 count.

PP increases in VLs have been attributed to physiological changes occurring during pregnancy, such as blood volume expansion and elevated levels of estrogen and progesterone, that do not persist after delivery. However, in our study, we did observe a difference in VLs PP according to whether ARVs were continued or discontinued following delivery (60% of women who received ARVs during pregnancy for PR had a VL increase).

The clinical implications of a VL increase in the PP period could be an increased risk of the development of viral resistance, possibly related to decreased adherence to ARVs in the PP period (Bardeguez et al. 2008). A recent analysis of data from the NISDI Perinatal Study included a predominantly asymptomatic population of HIV-infected pregnant women who were diagnosed with HIV infection during pregnancy and, therefore, only initiated ARVs during the index pregnancy (Duran et al. 2007). In this analysis, 14% of women had ARV resistance mutations at 6-12 weeks PP. The occurrence of resistance mutations was not associated with clinical, immunological or virological disease stage at the time points of comparison (enrollment and 6-12 weeks PP), nor with the most complex ARV regimens received during pregnancy. No significant association was found between VL and resistance mutations in this population of pregnant women.

A major strength of this study is the large size of the cohort, with enrollment at multiple sites. Also, enrollment occurred at clinical sites in six Latin American and Caribbean countries and the "country of residence" variable was retained in the multivariable model to account for heterogeneity attributable to differences in the study populations and practices. The period of PP follow-up was relatively short, which prevented the analysis of HIV disease progression after 6-12 weeks PP. Adherence to ARVs was not assessed as part of the protocol. However, the protocol has been modified to incorporate a longer follow-up PP (up to 5 years) and assessments of adherence.

The clinical implications of the observed VL and CD4% changes remain to be explored. However, it is important to emphasize that clinical disease stage remained quite stable throughout the duration of follow-up. Similarly, most women in the PR group maintained a CD4% $\geq$ 29% throughout the duration of follow-up. Whether the observed early increase in VL among those who used ARVs for the prevention of MTCT affects the risk of developing ARV-resistant viral mutations is an important question to assess, particularly in terms of the response to future ARV TR regimens.

APPENDIX

NICHD International Site Development Initiative: Perinatal/LILAC and Pediatric/Places Protocols - Principal investigators, co-principal investigators, study coordinators, coordinating center representatives, and NICHD staff include: Argentina: *Buenos Aires*: Marcelo H. Losso, Irene Foradori, Claudia Checa, Silvina Ivalo (Hospital General de Agudos José María Ramos Mejía); Brazil: *Belo Horizonte*: Jorge Pinto, *Victor Melo*, Fabiana Kakehasi (Universidade Federal de Minas Gerais); *Caxias do Sul*: Ricardo da Silva de Souza, *Nicole Golin*, Sílvia Mariani Costamilan (Universidade de Caxias do Sul/ Serviço Municipal de Infectologia); *Nova Iguaçu*: Jose Pilotto, *Beatriz Grinsztejn*, *Valdilea Veloso*, Gisely Falco (Hospital Geral Nova de Iguacu - HIV Family Care Clinic); *Porto Alegre*: Ricardo da Silva de Souza, *Breno Riegel Santos*, Rita de Cassia Alves Lira (Universidade de Caxias do Sul/Hospital Conceição); Ricardo da Silva de Souza, *Mario Ferreira Peixoto*, Elizabete Teles (Universidade de Caxias do Sul/Hospital Fêmina); Regis Kreitchmann, *Luis Carlos Ribeiro*, *Fabrizio Motta*, Debora Fernandes Coelho (Irmandade da Santa Casa de Misericordia de Porto Alegre); *Ribeirão Preto*: Marisa M. Mussi-Pinhata, *Geraldo Duarte*, *Adriana A. Tiraboschi Bárbaro*, *Conrado Milani Coutinho*, Anderson Sanches de Melo (Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo); *Rio de Janeiro*: Ricardo Hugo S. Oliveira, *Elizabeth S. Machado*, Maria C. Chermont Sapia (Instituto de Puericultura e Pediatria Martagão Gesteira); Esau Custodio Joao, Leon Claude Sidi, Ezequias Martins, Plinio Tostes Berardo (Hospital dos Servidores do Estado); *São Paulo*: Regina Celia de Menezes Succi, Prescilla Chow (Universidade Federal de São Paulo); Peru: *Lima*: Jorge Alarcón Villaverde (Instituto de Medicina Tropical "Daniel Alcides Carrión"- Sección de Epidemiología, UNMSM), *Carlos Velásquez Vásquez* (Instituto Nacional Materno Perinatal), César Gutiérrez Villafuerte (Instituto de Medicina Tropical "Daniel Alcides Carrión"- Sección de Epidemiología, UNMSM); Data Management and Statistical Center: Yolanda Bertucci, Laura Freimanis Hance, René Gonin, D. Robert Harris, Roslyn Hennessey, James Korelitz, Margot Krauss, Sharon Sothern de Sanchez, Sonia K. Stoszek (Westat, Rockville, MD, USA); NICHD: Rohan Hazra, Lynne Mofenson, Jennifer S. Read, Heather Watts, Carol Worrell (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, Maryland, USA).

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