Antiretroviral Adherence During Pregnancy and Postpartum in Latin America

Regis Kreitchmann, M.D., Ph.D.,[1] D. Robert Harris, Ph.D.,[2] Fabiana Kakehasi, M.D.,[3]
Jessica E. Haberer, M.D., M.S.,[4] Pedro Cahn, M.D.,[5] Marcelo Losso, M.D.,[6]
Elizabete Teles, B.S.N.,[7] Jose H. Pilotto, M.D., Ph.D.,[8] Cristina B. Hofer, M.D., Ph.D.,[9]
Jennifer S. Read, M.D., M.S., M.P.H.,[10,*] for the NISDI LILAC Study Team[†]

Abstract

Adherence to antiretrovirals by pregnant women (and postpartum women if breastfeeding) is crucial to effectively decrease maternal viral load and decrease the risk of mother-to-child transmission of HIV. Our objectives were to describe self-reported adherence to antiretrovirals during the antepartum (after 22 weeks of pregnancy) and postpartum periods (6–12 weeks and 6 months), and identify predictors of adherence among HIV-infected women enrolled and followed in a prospective cohort study from June 2008 to June 2010 at multiple sites in Latin America. Adherence was evaluated using the number of missed and expected doses during the 3 days before the study visit. At the pre-delivery visit, 340 of 376 women (90%) reported perfect adherence. This rate significantly decreased by 6–12 weeks (171/214 [80%]) and 6 months postpartum (163/199 [82%], $p < 0.01$). The odds for less than perfect adherence at the pre-delivery visit was significantly higher for pregnant women with current tobacco use (odds ratio [OR] = 2.9, 95% confidence interval [CI]: 1.46–6.14; p = 0.0029). At 6–12 weeks postpartum, the probability of non-perfect adherence increased by 6% for each 1 year increase in age (OR = 1.06, 95% CI: 1.00–1.12, p = 0.0497). At 6 months postpartum, the odds of nonperfect adherence was higher for those who were currently using alcohol (OR = 3.04, 95% CI: 1.34–6.90; p = 0.0079). Although a self-report measure of adherence based on only 3 days may lead to overestimation of actual adherence over time, women with perfect adherence had lower viral loads and higher CD4 counts. Adherence to antiretrovirals decreased significantly postpartum. Interventions should target women at high risk for lower adherence during pregnancy and postpartum, including tobacco and alcohol users.

Introduction

SUSTAINED, EFFECTIVE ANTIRETROVIRAL (ARV) therapy has been shown to transform HIV infection from a disease with limited options and a poor prognosis into a chronic infection with prolonged survival.[1] Adherence to ARVs is also crucial to optimize the clinical, immunologic, and virologic effectiveness of these drugs among pregnant women in order to prevent mother-to-child transmission (MTCT) of HIV.[2,3] Viral load has a strong direct correlation with the risk of

[1]Irmandade da Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil.
[2]Westat; Rockville, Maryland.
[3]Federal University of Minas Gerais, Belo Horizonte, Brazil.
[4]Massachusetts General Hospital, Boston, Massachusetts.
[5]Hospital General de Agudos Juan A. Fernandez, Buenos Aires, Argentina.
[6]Hospital General de Agudos Jose Maria Ramos Mejia, Buenos Aires, Argentina.
[7]Hospital Femina–Grupo Hospitalar Conceição, Porto Alegre, Brazil.
[8]Hospital Geral de Nova Iguaçu-HIV Family Care Clinic and Laboratório de AIDS e Imunologia Molecular (IOC) Fiocruz, Nova Iguaçú, Rio de Janeiro, Brazil.
[9]Instituto de Puericultura e Pediatria Martagão Gesteira and Department of Preventive Medicine–Univesidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.
[10]Pediatric, Adolescent, and Maternal AIDS Branch; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; Bethesda, Maryland.
*Current affiliation: NVPO/OASH/OS/DHHS; 200 Independence Avenue SW, Room 739G.6; Washington, D.C.
†Members of the NISDI LILAC Study Team are listed at the end of this article.

MTCT of HIV; therefore, the lower the maternal viral load, the lower the risk of MTCT of HIV. However, lowering maternal viral load is challenging since pregnancy is a relatively short time period in which to both initiate and adjust ARV regimens as necessary.

The effectiveness of ARV therapy is a function of the extent and duration of viral suppression, and it has been postulated that high levels of adherence ($\geq 90\%$) are necessary to achieve optimal treatment outcomes.[4] Factors associated with imperfect adherence to ARVs include factors associated with the patient (e.g., education about and commitment to ARV treatment, psychiatric illness, use of alcohol or other drugs), with treatment (e.g., adverse events, pill burden, and number of daily doses), and with the health care system (e.g., confidentiality). Any intervention to improve adherence must consider the patient holistically, i.e., taking into account behavioral, cognitive, emotional, and social characteristics.[5] However, relatively few studies of ARV adherence have included pregnant and postpartum women, and none were conducted in Latin America, although an estimated 1.4 million people were living with HIV infection in Latin America at the end of 2009, and slightly more than half of them were women and girls.[6]

Identification of HIV-infected women at greatest risk for nonadherence to ARVs during pregnancy and postpartum could help target resources for adherence counseling and support.

With this purpose in mind, adherence to ARVs during pregnancy and postpartum, as well as reasons for lack of adherence, was examined in a population of HIV-infected women at multiple sites in Latin America enrolled in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) prospective cohort study: Longitudinal Study in Latin American Countries (LILAC).

Materials and Methods

LILAC is a prospective cohort study of HIV-infected women and HIV-exposed, uninfected infants conducted at sites in Argentina, Brazil, and Peru,[7] with enrollment beginning in June 2008. The primary objectives of the LILAC study are: (1) to describe the characteristics of enrolled women and infants, including utilization of interventions for prevention of MTCT of HIV, use of ARVs, and rates of MTCT of HIV and (2) to characterize adverse events according to use of and exposure to ARVs and mode of delivery. Women are enrolled after 22 weeks of pregnancy and followed through delivery and postpartum. Maternal and infant study visits are conducted at hospital discharge after delivery, and then at 6–12 weeks and 6 months after delivery. Subjects are followed every 6 months thereafter, for up to 5 years after delivery/birth. Study visits include a medical history, a physical examination, and collection of laboratory samples. ARVs are prescribed according to local guidelines and self-reported adherence is recorded at each study visit (see below). The indication for use of ARVs during pregnancy (treatment of the mother's own HIV infection or prevention of MTCT of HIV) is recorded for each ARV regimen. Self-reported use (ever or current) of alcohol, tobacco, marijuana, cocaine/crack or heroin/opiates was recorded at study visits. The protocol was approved by the ethical review board at each clinical site, as well as by In-stitutional Review Boards at the sponsoring institution (NICHD) and at the data management center (Westat). All subjects provided written informed consent for participation in the study.

The study population for the present analysis comprised women enrolled in the LILAC study by June 30, 2010, during their first on-study pregnancy, who were prescribed ARVs for at least one of the three targeted visits (enrollment/ante-partum, 6–12 weeks postpartum, and 6 months postpartum) and for whom a self-report adherence form for the visit was completed. If the subject had both an enrollment visit and another, subsequent antepartum visit, then data at the later of the two visits was analyzed. The enrollment/antepartum visit is hereafter referred to as the pre-delivery visit. For viral load values below the limit of detection, the viral load value was set to half of the lower limit of detection for calculation of mean and median values (e.g., a viral load value of less than 400 copies/mL was reassigned a value of 200 copies/mL).

Percent adherence was derived using information available for all ARVs included in the subject's regimen at a particular study visit and considered doses missed yesterday, 2 days ago, and 3 days ago. The total number of doses missed was divided by the total number of expected doses to be taken for these three time periods for all of the ARVs included in the subject's regimen at the time of the visit; the measure was then expressed in the form of the percent adherence as follows:

$$Percent\ adherence = 100^* \left(1 - \left(\sum number\ of\ doses\ missed / \right. \right.$$
$$\left. \left. \sum expected\ number\ of\ doses \right) \right).$$

If the number of doses missed or the expected number of doses to be taken for a particular ARV for a particular time period (yesterday, 2 days ago, and 3 days ago) was missing, the adherence measure was set to missing. In instances where the reported number of doses missed for a visit was greater than the expected number of doses to be taken, the number of doses missed was set to the expected number of doses before calculating the adherence measures. An indicator of perfect adherence for each visit was derived from percent adherence to distinguish those that were 100% adherent over the 3-day time period from those that were not.

Information also was collected for a measure of long-term adherence that considered the last time an ARV dose was missed, as has been utilized previously.[8] The response options were: never, during the previous 2 weeks, during the last month, over a month ago, or do not remember.

Descriptive statistics were used to describe demographic and clinical characteristics of the study subjects, as well as the frequency and patterns of responses to the adherence measures. Generalized estimation equations (GEE) were used to compare pre-delivery to postpartum perfect adherence rates. Associations between subject characteristics and adherence were examined using bivariable techniques, such as Fisher's exact test for categorical-scaled measures and Student's *t* test and nonparametric procedures (Kruskal-Wallis test) for continuous measures. The associations of perfect adherence with subject characteristics were examined at the pre-delivery, 6- to 12-week postpartum, and 6-month postpartum visits for purposes of identifying predictors of adherence for possible

inclusion in multivariable modeling. Some subject characteristics were fixed at the time of enrollment, while information for others was updated at each study visit (e.g., substance use). For those characteristics that were measured at each visit, the value corresponding to the timing of the adherence measure was used in assessing the relationship to adherence (e.g., 6- to 12-week substance use for 6- to 12-week adherence analysis).

For a specific study visit, only those covariates associated with adherence at the $\alpha = 0.10$ level or less were considered as candidates for inclusion in the modeling, provided that their bivariable distributions would not lead to model failure due to small numbers or raise questions regarding the clinical importance of small differences between adherence groups. Logistic regression was used to model perfect adherence as a function of the characteristics meeting the above screening criteria, using forward stepwise selection.

Results

Size and characteristics of the study population

Among the 401 women enrolled in the LILAC study, none were enrolled for a second pregnancy on study. Five subjects were not prescribed ARVs at any of the three targeted visits, and another three did not complete the adherence form, even though they were prescribed ARVs at the time of the visit. Accounting for these exclusions, there were 393 subjects eligible for the study analyses at the pre-delivery visit (235 with the enrollment visit, but no subsequent antepartum visit; 158 with another antepartum visit after the enrollment visit). Characteristics of these 393 women are shown in Table 1. Of those using ARVs, 89.8% were using a three-drug regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI; 15.5%) or two NRTIs and one protease inhibitor (PI; 74.3%).

Antepartum and postpartum adherence to antiretrovirals

The number and proportion of women with a current prescription for ARVs and with a completed adherence form at each of the three visits was assessed. Of the 393 women with a pre-delivery visit, 383 had a current ARV prescription at that visit, and 376 had available adherence data. The mean adherence at the pre-delivery visit was 96.2% (standard deviation ([SD]: 15.8), and 340 women (90.4%) reported perfect adherence. Similarly, of the 383 women with a 6- to 12-week postpartum visit, 218 had a current ARV prescription at that visit, and 214 had available adherence data. The mean adherence at the 6- to 12-week postpartum visit was 89.1% (SD: 28.0), and 171 (79.9%) reported perfect adherence. Finally, of the 380 women with a 6-month postpartum visit, 206 had a current ARV prescription at that visit, and 199 had available adherence data. The mean adherence at the 6-month postpartum visit was 90.7% (SD: 25.0), and 163 women (81.9%) reported perfect adherence. Overall, percent adherence and the proportion of subjects with perfect adherence differed significantly across study visits when tested in the GEE model ($p \leq 0.0065$; data not shown). Additionally, postpartum adherence was significantly lower than antepartum adherence ($p \leq 0.0082$), but adherence did not vary significantly between the 6- to 12-week and 6-month postpartum visits ($p > 0.49$; data not shown). Similar findings were observed when the models were fit to the data restricted to subjects with adherence measured at all three study visits.

Factors associated with perfect adherence to antiretrovirals

Table 2 presents the results of bivariable analyses of perfect adherence for each of the three time periods. At the pre-delivery visit, the following factors were associated with perfect adherence: mode of acquisition of HIV infection, CD4 percent, viral load, substance abuse (ever), current use of alcohol, current use of tobacco, and duration of use of ARVs. Due to small numbers of subjects with modes of acquisition of HIV infection other than heterosexual transmission, this variable was not considered a candidate variable for multivariable modeling. CD4 percent and viral load were considered to more likely be outcomes of adherence rather than risk factors for nonperfect adherence; therefore, these variables were not included in multivariable modeling. The remaining four variables (substance use [ever], current use of alcohol, current use of tobacco, and duration of use of ARVs] were candidate variables for the pre-delivery adherence model, but only current tobacco use remained in the model based on forward stepwise selection. The probability of nonperfect adherence was almost three times higher among those with current use of tobacco than among those not currently using tobacco (odds ratio [OR] = 2.9; 95% confidence interval [CI]: 1.46–6.14; $p = 0.0029$).

The following factors were associated with perfect adherence at the 6- to 12-week postpartum visit: age, parity, and viral load. As delineated above, since viral load was considered more likely to represent an outcome of adherence rather than a risk factor for nonperfect adherence, this variable was not included in multivariable modeling. Thus, age and parity were candidate variables for the 6- to 12-week postpartum adherence model, but only age was independently associated with adherence. The probability of nonperfect adherence increased by 6% for each 1-year increase in age (OR = 1.06; 95%CI: 1.00–1.12; $p = 0.0497$).

Variables associated with perfect adherence at the 6 month postpartum visit included: parity, education, number of persons living in the household, mode of acquisition of HIV infection, CD4 count, viral load, current use of alcohol, current use of tobacco, and CDC immunologic classification. As before, CD4 count, viral load, and CDC immunologic classification (based on CD4 count) were considered outcomes of adherence rather than risk factors for nonperfect adherence and not included in multivariable modeling. Thus, the remaining five variables (parity, education, number of persons living in the household, current use of alcohol, current use of tobacco) were candidate variables for multivariable modeling, but only current use of alcohol was independently associated with adherence. The probability of non-perfect adherence was over threefold higher for those who were currently using alcohol at the time of the 6-month visit (OR = 3.04; 95% CI: 1.34–6.90; $p = 0.0079$).

Percent adherence and plasma viral load

As noted above, plasma viral load was considered an outcome of adherence rather than a risk factor for nonperfect

Table 1. Characteristics of Study Population ($N=393$) at the Pre-Delivery (Enrollment/Antepartum) Visit

Characteristic	n (%)	Mean (SD) median
Country		
Brazil	312 (79.4)	
Argentina	37 (9.4)	
Peru	44 (11.2)	
Age at enrollment (years)		29.0 (6.0)
		29.0
Race		
Black of African heritage	83 (21.1)	
White	180 (45.8)	
Mestizo/Mulato	130 (33.1)	
Parity		
0	70 (17.8)	
1–2	213 (54.2)	
>2	110 (28.0)	
Educational level (years completed)		8.3 (3.2)
		8.0
Number of persons living in subject's household		4.0 (2.0)
		4.0
Gainfully employed outside of home		
Yes	142 (36.1)	
No	251 (63.9)	
Mode of acquisition of HIV infection		
Heterosexual transmission with or without other modes	365 (92.9)	
Other	5 (1.3)	
Unknown	23 (5.9)	
CD4 count at visit (cells/mm³)		499.6 (273.1)
		470
CD4 absolute count at visit (cells/mm³)		
<200	51 (13.0)	
200–499	158 (40.2)	
≥500	184 (46.8)	
CD4% at visit:		28.7 (10.5)
		29.0
Missing	*64*	
CD4% at visit		
<14%	24 (7.3)	
14–28%	131 (39.8)	
>28%	174 (52.9)	
Missing	*64*	
Viral load at visit (copies/mL)		5478 (30,445)
		200
Viral load at visit ($\log_{10}$ copies/mL)		2.37 (0.86)
		2.30
Viral load at visit (copies/mL)		
<400 (includes "below detection limit")	306 (78.1)	
≥400	86 (21.9)	
Substance use—ever		
Ever used substances	206 (52.6)	
Never	186 (47.4)	
Substance use—current		
Alcohol	71 (18.1)	
Tobacco	88 (22.4)	

Table 1. (Continued)

Characteristic	n (%)	Mean (SD) median
Marijuana	16 (4.1)	
Cocaine/crack	17 (4.3)	
Heroin/opiates	7 (1.8)	
Hospitalized in last year or since last study visit		
Yes	27 (6.9)	
No	366 (93.1)	
Duration of HIV diagnosis at visit (years)		2.4 (3.1)
		1.0
ARV history at visit: n (%)		
ARV-naïve	9 (2.3)	
ARV-experienced	384 (97.7)	
ARV regimen: *n* (%)		
None	12 (3.1)	
1 NRTI	4 (1.0)	
2 NRTIs + 1 NNRTI	59 (15.0)	
2 NRTIs + 1 PI	283 (72)	
Other	35 (8.9)	
Duration of use of ARVs at visit (months)		13.9 (22.9)
		4.0
Reason for ARV use at visit		
Prophylaxis	203 (53.0)	
Treatment	180 (47.0)	
Current CDC clinical classification		
A	323 (82.2)	
B	34 (8.7)	
C	36 (9.2)	
Current CDC immunologic classification		
Category 1 (CD4 ≥ 500 cells/mm³; CD4% ≥ 29%)	117 (29.8)	
Category 2 (CD4 200–499 cells/mm³; CD4% 14–28%)	177 (45.0)	
Category 3 (CD4 < 200 cells/mm³; CD4% < 14%)	99 (25.2)	
Current WHO clinical classification		
Stage 1	348 (88.5)	
Stage 2	15 (3.8)	
Stage 3	16 (4.1)	
Stage 4	14 (3.6)	
Current WHO immunological classification		
None or not significant (CD4 > 500 cells/mm³)	168 (42.9)	
Mild (CD4 350–499 cells/mm³)	75 (19.1)	
Advanced (CD4 200–349 cells/mm³)	89 (22.7)	
Severe (AIDS) (CD4 < 200 cells/mm³)	60 (15.3)	

ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; CDC, Centers for Disease Control and Prevention; SD, standard deviation; WHO, World Health Organization.

TABLE 2. CHARACTERISTICS ASSOCIATED WITH PERFECT ADHERENCE TO ANTIRETROVIRALS AT THE PRE-DELIVERY, 6- TO 12-WEEK POSTPARTUM, AND 6-MONTH POSTPARTUM VISIT

Characteristic	Perfect adherence at pre-delivery			Perfect adherence at 6–12 weeks postpartum			Perfect adherence at 6 months postpartum		
	Yes (N=340)	No (N=36)	p Value[a]	Yes (N=171)	No (N=43)	p Value[a]	Yes (N=163)	No (N=36)	p Value[a]
Age (years)									
Mean (SD)	29.0 (6.0)	29.8 (6.1)	0.45	29.5 (6.1)	31.5 (5.0)	0.06	30.4 (5.9)	29.6 (5.5)	0.47
Median	29.0	28.5		29.0	31.0		30.0	30.0	
Parity: n (%)									
0	61 (91.0)	6 (9.0)	0.42	31 (83.8)	6 (16.2)	0.08	35 (94.6)	2 (5.4)	0.04
1–2	190 (91.8)	17 (8.2)		99 (83.9)	19 (16.1)		87 (81.3)	20 (18.7)	
>2	89 (87.3)	13 (12.7)		41 (69.5)	18 (30.5)		41 (74.5)	14 (25.5)	
Education (years completed)									
Mean (SD)	8.2 (3.3)	8.5 (2.8)	0.61	8.4 (3.2)	8.4 (2.9)	0.95	8.7 (3.1)	7.6 (3.4)	0.06
Median	8.0	8.0		8.0	8.0		8.0	8.0	
Number of persons living in subject's household									
Mean (SD)	4.0 (2.1)	4.0 (2.5)	0.93	4.1 (2.4)	4.0 (2.3)	0.87	4.0 (2.4)	4.6 (2.4)	0.08
Median	4.0	3.0		4.0	4.0		3.0	4.0	
Mode of HIV infection									
Heterosexual transmission with or without other modes of transmission	322 (91.2)	31 (8.8)	0.03	159 (81.1)	37 (18.9)	0.13	154 (83.2)	31 (16.8)	0.05
Other	3 (60.0)	2 (40.0)		3 (100)	0		3 (100)	0	
Unknown	15 (83.3)	3 (16.7)		9 (60.0)	6 (40.0)		6 (54.5)	5 (45.5)	
CD4 count (cells/mm^3) at visit									
Mean (SD)	510.8 (272.6)	456.6 (262.8)	0.26	531.5 (275.6)	482.6 (275.3)	0.30	520.7 (257.3)	495.2 (429.6)	0.06
Median	486.0	426.5		485.5	408.0		494.0	370.5	
CD4 count (cells/mm^3) at visit									
<200	39 (83.0)	8 (17.0)	0.20	14 (73.7)	5 (26.3)	0.36	15 (71.4)	6 (28.6)	0.10
200–499	137 (91.3)	13 (8.7)		74 (77.1)	22 (22.9)		69 (78.4)	19 (21.6)	
≥500	164 (91.6)	15 (8.4)		82 (83.7)	16 (16.3)		79 (87.8)	11 (12.2)	

(continued)

TABLE 2. (CONTINUED)

Characteristic	Perfect adherence at pre-delivery			Perfect adherence at 6–12 weeks postpartum			Perfect adherence at 6 months postpartum		
	Yes (N=340)	No (N=36)	p Value[a]	Yes (N=171)	No (N=43)	p Value[a]	Yes (N=163)	No (N=36)	p Value[a]
CD4% at visit:									
Mean (SD)	29.3 (10.4)	24.6 (10.4)	**0.03**	26.2 (9,7)	23.9 (8.5)	0.20	26.3 (8.5)	29.8 (28.2)	0.50
Median	30.0	25.5		25.0	24.5		27.0	23.0	
CD4% at visit: n (%)									
<14%	18 (81.8)	4 (18.2)	**0.07**	13 (72.2)	5 (27.8)	0.50	12 (66.7)	6 (33.3)	0.16
14–28%	112 (91.1)	11 (8.9)		79 (80.6)	19 (19.4)		78 (85.7)	13 (14.3)	
>28%	161 (94.7)	9 (5.3)		61 (83.6)	12 (16.4)		62 (84.9)	11 (15.1)	
CDC immunologic classification: n (%)									
Category 1	100 (89.3)	12 (10.7)	0.52	18 (90.0)	2 (10.0)	0.59	16 (94.1)	1 (5.9)	**0.08**
Category 2	156 (92.3)	13 (7.7)		80 (79.2)	21 (20.8)		76 (86.4)	12 (13.6)	
Category 3	84 (88.4)	11 (11.6)		73 (78.5)	20 (21.5)		71 (75.5)	23 (24.5)	
Viral load ($\log_{10}$ copies/mL) at visit									
Mean (SD)	2.3 (0.7)	2.5 (1.1)	0.22	2.3 (0.9)	2.9 (1.4)	0.06	2.4 (1.0)	3.0 (1.4)	**0.01**
Median	2.3	2.3		2.3	2.3		2.3	2.6	
Viral load (copies/mL) at visit: n (%)									
<400	282 (92.5)	23 (7.5)	**0.01**	140 (84.8)	25 (15.2)	**0.002**	128 (87.1)	19 (12.9)	**0.003**
≥400	57 (81.4)	13 (18.6)		31 (63.3)	18 (36.7)		35 (67.3)	17 (32.7)	
Substance use—ever: n (%)									
Yes	171 (87.2)	25 (12.8)	**0.04**	92 (75.4)	30 (24.6)	0.39	84 (76.4)	26 (23.6)	0.27
No	168 (93.9)	11 (6.1)		33 (82.5)	7 (17.5)		35 (85.4)	6 (14.6)	
Alcohol use—current: n (%)									
Yes	54 (80.6)	13 (19.4)	**0.005**	19 (73.1)	7 (26.9)	0.43	23 (65.7)	12 (34.3)	**0.01**
No	286 (92.6)	23 (7.4)		152 (80.9)	36 (19.1)		140 (85.4)	24 (14.6)	
Tobacco use—current: n (%)									
Yes	68 (81.0)	16 (19.0)	**0.002**	28 (75.7)	9 (24.3)	0.50	25 (67.6)	12 (32.4)	**0.02**
No	272 (93.2)	20 (6.8)		143 (80.8)	34 (19.2)		138 (85.2)	24 (14.8)	
Duration of use of ARVs at visit (in months)									
Mean (SD)	14.7 (23.1)	10.5 (22.6)	**0.03**	25.8 (27.6)	22.3 (27.4)	0.47	32.0 (29.2)	26.6 (24.2)	0.30
Median	4.0	3.0		13.0	8.0		19.0	18.5	

[a]The p values for continuous characteristics were obtained from the Student's t test and nonparametric testing (Kruskal-Wallis test); p values for categorical characteristics are based on Fisher's exact test.

SD, standard deviation; ARVs, antiretrovirals.

adherence. Further analyses of the association between percent adherence and plasma viral load were conducted utilizing data from 375, 214, and 199 women at the pre-delivery, 6- to 12-week postpartum, and 6-month postpartum visits, respectively. At the pre-delivery visit, 70 women with a detectable viral load (≥ 400 copies per milliliter) had a mean adherence of 88.6 (SD: 29.3) and 305 with a nondetectable viral load had a mean adherence of 97.9 (SD: 9.9; $p = 0.0029$). Similarly, at the 6- to 12-week postpartum visit, 49 women with a detectable viral load had a mean adherence of 70.1 (SD: 44.5) and 165 with a nondetectable viral load had a mean adherence of 94.7 (SD: 17.3; $p = 0.0001$). Finally, at the 6 month postpartum visit, 52 women with a detectable viral load had a mean adherence of 80.1 (SD: 36.2) and 147 with a nondetectable viral load had a mean adherence of 94.5 (SD: 18.3; $p = 0.0008$). Thus, at each time point, those women with detectable viral loads had lower mean percent adherence.

Reasons for nonperfect adherence

Subjects reporting that they had any problems or situations making it difficult to take every dose of medication every day were asked to respond to a list of different problems or situations related to ARV adherence (Table 3). The most common problem related to taking ARVs was forgetting to take the ARV (35.8% pre-delivery, 52.0% at 6–12 weeks postpartum, and 64.5% at 6 months postpartum). The other commonly cited reasons were: being away from home, a change in the daily routine, and running out of ARVs/not coming for ARVs.

Last time antiretrovirals were missed during and after pregnancy

At the pre-delivery visit, when asked about the last time medications were missed, 67.8% of women responded that they never forgot their medication. By the time of the 6- to 12-week and 6-month postpartum visits, 55.6% and 57.2% of women responded that they never forgot their medications, respectively. Long-term adherence varied over time ($p = 0.0004$), with significant differences identified between the pre-delivery visit and the 6- to 12-week and 6-month postpartum visits; long-term adherence did not differ between postpartum visits.

Discussion

In this analysis of ARV adherence among pregnant and postpartum women in Latin America, there was a statistically significant decline in perfect adherence to ARVs during the postpartum period (80% at 6–12 weeks and 82% at 6 months) compared to reported adherence during pregnancy (90.4%). Current tobacco use was a predictor of non-perfect adherence to ARVs during pregnancy, and older age and current alcohol use were associated with nonperfect adherence at 6–12 weeks and 6 months postpartum, respectively. Our results confirm the association described previously between ARV adherence as measured by the simple and low-cost approach of self-report and positive clinical, immunologic, and virologic outcomes.[9,10–13] That said, a self-report measure of adherence based on only 3 days may lead to overestimation of actual adherence over time.[14] A very common reason for missing ARV doses cited by women was "just forgot." However, this response may be a euphemism for some other situations associated with taking/giving medications (e.g., stigma, depression) that the participants do not want to discuss.

The adherence rates we observed among the study population during pregnancy and postpartum are similar to what has been reported in some studies,[15] but higher than reported by others.[16–18] However, all of these mentioned studies, as well as ours, reported higher adherence rates during pregnancy compared to postpartum. The differences between studies may reflect differences in population characteristics, access to care, and the complexity of ARV regimens used. Most subjects in our study used PI-containing regimens, with dosing schedules that required relatively few pills each day.

Substance use appears to be an important factor in ARV adherence during and after pregnancy. The rates of using alcohol (18.1%) and tobacco (22.4%) during pregnancy observed in our study population were higher than anticipated but were not different from what was observed postpartum, contrary to the expectation that women tend to have less substance use during pregnancy. The association between tobacco and alcohol use and nonperfect adherence has been previous reported.[15,17,18] One recent study comparing HIV-infected female smokers to nonsmokers demonstrated increased mortality and decreased adherence to ARV treatment among current smokers.[19] Several additional studies showed lower rates of virologic suppression in HIV-infected smokers compared to nonsmokers, and speculated that inferior adherence could have been a contributing factor.[20,21] The reasons for poorer adherence among smokers are not precisely defined. Cigarette smoking is frequently linked to other behaviors that have been considered predictors of nonadherence, such as depression[22–24] and illicit substance use.[25,26] Possible reasons for poorer adherence to ARV treatment among HIV-infected smokers include indifference to health outcomes,[27] a propensity for risk taking,[28] and fatalism.[29]

An unexpected finding in our study was the association of older age with nonadherence at 6- to 12-week postpartum visit. Poorer ARV adherence among adolescents, even during pregnancy has been described.[30] However, adolescents were under-represented in our study. Some studies have shown that HIV-infected women with children under 18 years old living with them experience increased demands compared to HIV-infected women without children, which subsequently results in poorer adherence to antiretrovirals.[31,32] The association between older age and nonadherence in our study needs further exploration.

The strengths of our study include its prospective cohort study design, with questionnaires included to evaluate adherence. Our self-report measure is simple and low cost to implement, and correlated with viral load in this relatively high adherence population. Additionally, we evaluated adherence at two time points during the postpartum period, allowing us to examine changes in behavior during this complex time in women's lives. A limitation of the study is that it did not include measures of psychosocial factors, such as depression, stressful life events and time constraints, nor did it include objective measures of adherence. Additionally, the small numbers of women reporting hard drug use may have limited the power to assess this factor's association with adherence.

TABLE 3. PROBLEMS OR SITUATIONS MAKING IT DIFFICULT TO TAKE ANTIRETROVIRALS IN EACH STUDY VISIT

Problem or situation making it difficult to take ARVs	Instances where problem identified		
	Pre-delivery visit (n = 293)	6- to 12-week postpartum visit (n = 152)	6-month postpartum visit (n = 138)
Just forgot	105	79	89
Subject was away from home	70	21	16
I ran out of medicine; didn't come for medicine	32	28	30
There was a change in daily routine	47	22	34
Was worried about side effects	22	11	11
Subject was busy with other things	13	12	8
Medicine tastes bad	10	5	5
Too busy with baby/child	0	23	15
Did not want others to notice caregiver giving the medicine	8	0	2
Baby/child was ill	1	0	1
Family said someone told them not to give/take the medicine	0	0	0
Study subject was ill	13	0	0
Subject felt depressed	9	7	10
There was too much medicine to give	0	2	0
Other problems or situations	39	34	16

The results of this study confirm previous reports that women are more likely to adhere to ARVs during pregnancy than postpartum. This study highlights the vulnerability of HIV-infected women during the postpartum period and the need to design and evaluate adherence interventions containing a substance use cessation component. Although improved adherence during pregnancy has been critical to the successful reduction of MTCT of HIV, these successes will be tempered by increased maternal morbidity and mortality and a potential increase in orphans if we fail to implement interventions to maintain adherence to ARVs over the long term. Substance use cessation during gestation has well-known additional benefits from the neonatal perspective and should be a major goal in prenatal care.[33,34] Interventions to provide adequate social support and integration with mental health programs should be explored as means to help women to adhere to ARVs.

Author Disclosure Statement

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Address correspondence to:
Regis Kreitchmann, M.D., Ph.D
Health Secretary
STD/AIDS Municipal Center
Manoel Lobato 151
Porto Alegre
Rio Grande do Sul
Brazil

E-mail: regis.kr@terra.com.br