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Predictors of Adverse Pregnancy Outcomes in HIV infected Women in Latin America and the Caribbean: a Cohort Study

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Abstract

Objectives—To examine maternal characteristics associated with adverse pregnancy outcomes (APOs) among HIV-infected women.

Design—Prospective cohort study

Setting—Multiple sites in Latin America and the Caribbean

Population—First on-study pregnancy among HIV-1-infected women enrolled in NISDI (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative) Perinatal (2002–2007) and LILAC (2008–2012) studies.

Methods—Frequencies of APOs assessed among pregnancies. Risk factors investigated by logistic regression analysis.

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Ethics Approval
The protocols were approved by the ethical review board at each participating site as well as by institutional review boards at the sponsoring institution (NICHD) and at the data management and statistical center (Westat).

Contribution to Authorship
SL carried out the statistical analysis, with support from RK, and drafted the paper. RK, VHM, DFC, EJ, CMC, and JOA provided clinical management to study patients. HW, GKS and all the previous mentioned authors contributed to the interpretation of the results, commented on all drafts of the paper, and approved the final version.

Disclosure of interests
The authors have no interests to declare.

Main Outcome measures—APOs including preterm delivery (PT), low birth weight (LBW), small for gestational age (SGA), stillbirth (SB) and neonatal death.

Results—Among 1512 women, 1.9% (95% confidence interval [CI] 1.3–2.7%) of singleton pregnancies resulted in a stillbirth and 32.9% (30.6–35.4%) had at least one APO. Of 1483 singleton live births, 19.8% (17.8–21.9%) were PT, 14.2% (12.5–16.1%) were LBW, 12.6% (10.9–14.4%) were SGA, and 0.4% (0.2–0.9%) of infants died within 28 days after birth. Multivariable logistic regression modeling indicated that the following risk factors increased the probability of having one or more APOs: lower maternal body mass index (odds ratio [OR]=2.2; 95% CI: 1.4–3.5) at delivery, hospitalization during pregnancy (OR=3.3; 95% CI: 2.0–5.3), hypertension during pregnancy (OR=2.7; 95% CI: 1.5–4.8), antiretroviral use at conception (OR=1.4; 95% CI: 1.0–1.9) and tobacco use during pregnancy (OR=1.7; 95% CI: 1.3–2.2). Results of fitting multivariable logistic regression models for PT, LBW, SGA and SB are also reported.

Conclusions—HIV-infected women had relatively high occurrence of APOs and some maternal risk factors were associated with these APOs. Interventions targeting modifiable risk factors should be evaluated further.

Keywords

HIV; pregnancy; pregnancy outcomes; prematurity; Latin America

Introduction

The HIV epidemic has affected millions of women of child-bearing age worldwide. HIV mother to child transmission (MTCT) has been drastically reduced by means of universal testing for pregnant women, antiretroviral (ARV) treatment, use of elective cesarean delivery for women without viral suppression, and, in settings like Latin America, avoidance of breastfeeding.(2)

Besides HIV MTCT, other adverse pregnancy outcomes (APOs), such as preterm deliveries (PT), low birth weight (LBW), small for gestational age (SGA), stillbirths and neonatal deaths have been frequently reported among pregnancies complicated by HIV.(3–5)

It has been known that SGA, LBW and PT are associated with increased neonatal mortality and significant long term morbidity, including neurocognitive deficits, chronic respiratory and metabolic problems.(6–9)

Some of the predictors for these outcomes have been described but there is limited information from Latin America in the era of routine use of highly active ARV therapy (HAART).

Identifying the risk factors for APOs among HIV-infected women will help to allocate resources to interventions that may prevent these APOs in the future.

Methods

Study design and population

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal Study (2002–2007) and the subsequent Longitudinal Study in Latin American Countries (LILAC) Study (2008–2012) are prospective cohort studies of HIV-infected pregnant women and their infants at participating clinical sites in Latin America and the Caribbean.(10) These protocols were designed to describe characteristics of enrolled pregnant women and their infants, including the utilization of interventions to decrease the risk of HIV MTCT, use of ARV regimens, and maternal adverse events according to the use of ARVs. Women enrolled in the study were followed during pregnancy, through delivery, at hospital discharge, and 6–12 weeks postpartum. During each study visit, the participants' clinical, immunologic, and virologic characteristics were assessed through a physical examination, evaluations of laboratory results and a review of medical diagnoses experienced since the last visit. Prior to enrollment, all participants signed an approved informed consent for study participation.

Pregnant women who were enrolled in the NISDI Perinatal and LILAC protocols and met the following criteria were included in the current analyses: first on-study, pregnancy with an outcome as either a live birth or a stillbirth. If a woman enrolled in both protocols, the first pregnancy in the Perinatal protocol was chosen.

Outcome measures and risk factors

Gestational age (GA) was assessed by obstetricians using ultrasound, last menstrual period and fundal height measurements. Adverse pregnancy outcomes of interest were derived using the following definitions: preterm delivery (PT) defined as a birth with GA below 37 completed weeks; very preterm delivery defined as a birth with GA below 32 completed weeks; low birth weight (LBW) defined as a birth weight (BW) below 2500 grams; very low birth weight (VLBW) defined as a BW below 1500 grams; small for gestational age (SGA) defined as BW below the 10^{th} percentile of a referent infant population at the same gestational age;(11) neonatal death defined as the death of a liveborn infant in the first 28 days of life; and stillbirth defined as a birth at the twentieth week of gestation or later, with no signs of life. A composite variable, adverse pregnancy outcomes (APOs), was defined as the presence of one or more of the adverse pregnancy outcomes described above.

Socio-demographic, clinical and laboratory characteristics and obstetrical history, including previous preterm birth or stillbirth among the recruited pregnant women, were collected at enrollment. The HIV disease status was evaluated throughout the study, including CD4 count, plasma HIV-1 RNA concentration and CDC HIV clinical classification. Medications (ARV and non-ARV) taken by the participants were documented at each study visit including drug names and start and stop dates. ARV use was categorized as: any ARV use; duration of ARV therapy during pregnancy; receipt of ARVs at conception; and reason for receiving ARVs during pregnancy (treatment versus prophylaxis according to local guidelines). For purposes of analysis, ARV regimens were classified into three different timeframes during pregnancy: most complex regimen received for ≥28 days during the

entire pregnancy and most complex regimen received for ≥28 days during the first or third trimester of pregnancy. The regimens were categorized as: HAART with a protease inhibitor (HAART PI), HAART without a PI (HAART not PI), and non-HAART regimens; where relevant, participants were categorized as not receiving ARVs or not receiving a particular regimen for at least 28 days. HAART was defined as at least three different ARVs (except for ritonavir if used as a booster) from at least two distinct drug classes.

Prophylaxis for opportunistic infection during pregnancy was defined as receiving isoniazid (INH) during pregnancy in absence of other drugs for tuberculosis (TB) infection or receiving TMP-SMX (trimethoprim-sulfamethoxazole) for at least 2 weeks during pregnancy for *Pneumocystis* pneumonia (PCP) prophylaxis.

Maternal substance abuse during pregnancy was recorded through maternal interview at enrollment. The presence of hypertension during pregnancy was defined on the basis of a diagnosis of eclampsia (seizures complicating hypertension during pregnancy), pre-eclampsia (hypertension after 20 weeks of pregnancy and proteinuria), pregnancy-induced hypertension (hypertension after 20 weeks of pregnancy without proteinuria) or chronic hypertension (hypertension preceding current pregnancy or new-onset before 20 weeks). Diabetes was defined on the basis of a new, ongoing or resolved diagnosis of type I or II diabetes, gestational diabetes or pre-gestational diabetes reported in the medical record.

Statistical methods

Prevalence of the defined adverse pregnancy outcomes in the study population was computed with 95% confidence intervals (CIs) based on a binomial distribution. Contingency table analyses were used to examine associations of study outcomes with each of the risk factors; p-values were calculated using the Fisher's exact or Fisher-Freeman-Halton exact test for categorical variables. The nonparametric Wilcoxon test was used to calculate p-values for continuous variables. Missing values were excluded from the statistical tests.

Adjusted logistic regression analyses for each outcome started with a base model including all marginally significant candidate risk factors (p-values <0.1) from the bivariate analyses. Among variables that were highly correlated, the one identified as the stronger predictor was included in the base model. Additional models fit to the data to explore risk factors associations were compared using fit statistics (likelihood ratio test, Akaike's information criterion (AIC), c statistic and goodness-of-fit test) to identify the best fitting model to the data.

All p-values were two-sided with p-values less than 0.05 being considered statistically significant. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Of 1630 enrolled pregnant women, 1563 had first on-study pregnancies, including 1533 who had live-born infants and 30 who had stillbirths. Six out of 1533 live births had no birth

weight recorded, resulting in a total of 1527 mother-infant pairs eligible for the initial analyses with birth weight-related study outcomes.

Among 1483 participants who had live singleton births, 293 (19.8%) pregnancies resulted in preterm deliveries (95% CI: 17.8 – 21.9%), and 30 (2.0%) were very preterm deliveries (Table 1). Among 1477 participants for whom birth weight was available, 210 (14.2%) live births were low birth weight infants (95% CI: 12.5 – 16.1%), 19 (1.3%) were very low birth weight, and 186 (12.6%) were SGA (95% CI: 10.9 – 14.4). Six (0.4%) infants died within 28 days of birth (95% CI: 0.2 – 0.9%). Among the entire study population of singleton births, 29 (1.9%) pregnancies resulted in a stillbirth (95% CI: 1.3 – 2.7). A total of 498 (32.9%) participants had at least one adverse pregnancy outcome (95% CI: 30.6 – 35.4). Table 1 also presents the prevalence of the study outcomes among all births and multiple births only; given the small number of multiple births and the difficulties this would pose for the analyses, models were not fit for these groups. Since the numbers of outcomes of very preterm delivery, very low birth weight and neonatal death were very small, no further analysis was performed for these outcomes either.

Most participants were enrolled in Brazil (62.8%) and Argentina (24.5%) with smaller numbers in the Bahamas (2.8%), Jamaica (2.4%), Mexico (2.8%) and Peru (4.6%). The average age at delivery for these participants was 28.2 years (SD=5.9) and completed education was 8.0 years (SD=3.2) on average. Among 815 participants who reported their ethnicity, 745 (91.4%) were Hispanic/Latino and 70 were either non-Hispanic/ Latino or ethnicity unknown. Among 804 participants who reported their race, 58.0% were white, 20.4% were black and 21.6% were other races. A thorough description of the characteristics of the participants with singleton births, including examination of the relationship of the characteristics with APOs, is provided in the Table S1 posted on-line (*on-line location*). In brief, risk factors for APOs that were explored in bivariate analyses included maternal age, BMI, history of stillbirths and preterm births, HIV disease characteristics (CD4+ lymphocyte count, plasma HIV RNA, ARV use during pregnancy, CDC clinical classification), substance use during pregnancy (alcohol, tobacco marijuana and crack/ cocaine), hospitalization during pregnancy, and maternal diagnoses during pregnancy (anemia, urinary tract infection, upper and lower respiratory tract infections, syphilis and hypertension during pregnancy).

Risk factors that were included in the final multiple logistic regression models for each of the adverse pregnancy outcomes are summarized in Table 2. For the composite variable of any adverse pregnancy outcome (APOs), lower BMI at delivery (<18.5 kg/m^2) increased the probability of APOs (OR=2.23, 95% CI: 1.43 – 3.46) while higher BMI (≥25 kg/m^2) decreased the probability (OR=0.63, 95% CI: 0.48 – 0.84). A similar relationship with BMI was also observed for LBW and SGA. Hospitalization during pregnancy was associated with APOs (OR=3.25, 95% CI: 1.98 – 5.34), as well as with PT and LBW. Hypertension during pregnancy was associated with a 2.7-fold increased risk of APOs, with similar increased risks observed for LBW and SGA. There was a 40% increased risk of APOs (primarily from PT) associated with receipt of ARVs at conception. Tobacco use during pregnancy increased the risk of any adverse pregnancy outcome by 71%, and by 78% specifically for SGA. Although not associated with risk of APOs, women diagnosed with a lower respiratory tract

infection during pregnancy had a significantly increased risk of PT and SB (OR=2.34, 95% CI: 1.03 – 5.31 and OR-4.13, 95% CI: 4.13 – 15.58, respectively).

Discussion

Main findings

We report the results of the largest study to date on adverse pregnancy outcomes among HIV-infected women in Latin America. The findings indicate a substantial burden of adverse pregnancy outcomes with prevalence of PT, LBW, and SGA infants of 19.8%, 14.2%, and 12.6%, respectively, and prevalence of SB and neonatal death of 1.9% and 0.4%, respectively. The rates of these adverse outcomes among HIV-infected pregnant women, consistent with prior studies, are higher than those among HIV negative women. (13, 14)

Strengths and limitations

The primary limitation of this study is the lack of a comparison group of HIV-uninfected pregnant women, which would have strengthened the study by allowing a more thorough investigation of risk factors associated with the study outcomes. The NISDI study was designed to characterize adverse events among HIV-1-infected women and their infants according to ARV exposure. HIV-negative pregnant women were not included in the original study design and budgetary constraints would not allow for a sample of HIV-uninfected pregnant women to be enrolled at a later time for this investigation. Our analyses should therefore be interpreted as identifying risk factors for adverse pregnancy outcomes among HIV-infected pregnant women.

The use of US-based data for defining SGA in this setting may have led to errors in estimation. However, the exact extent and direction of these errors would be difficult to quantify given the relationship between birth weight and gestational age according to ethnicity found in US studies; when available in US studies, birth weight is generally found to be higher among Hispanics than among white, non-Hispanics up to about 37 weeks gestation, after which it is higher for white, non-Hispanics. [10]

This study offers the advantage of having collected data on a large prospective cohort of HIV-infected women in Latin America from multiple participating sites, which provided good statistical power for the analyses of most study outcomes. Even so, small numbers of neonates with birth weights below 1500 grams and small numbers born before 32 weeks of gestation limited our ability to evaluate these important outcomes further.

Data was collected using standardized case report forms, better ensuring comparability of data collection across the multiple sites and across time as participants were enrolled and followed on-study. Unfortunately, detailed information was not collected on the reasons for hospitalization in order to analyze this risk factor further.

Interpretation

The association of antiretroviral exposure at the time of conception with adverse pregnancy outcomes is similar to what has been previously described.(15–19) Previous studies of

adverse pregnancy outcomes related to the effect of HAART have reported conflicting results depending on the timing and type of antiretroviral therapy, which may be confounded by other maternal risk factors in pregnancy.(1, 17, 18, 20–24) Compared to ARV use for prophylaxis, use of antiretrovirals for treatment was associated with the occurrence of LBW, possibly as a proxy of maternal disease stage. The pathogenesis of preterm labor and the potential increased risk among HIV infected women are not well understood. The inflammatory changes of immune reconstitution syndromes could play a role in women who started HAART at a low CD4 count but other mechanisms may be involved in women with higher CD4. Systemic or local genital tract immunology might be affected by ARVs and precipitate preterm labor, or induced changes in systemic cytokines could exacerbate hypertensive disorders and lead to preterm birth.(25, 26)

We also found that the use of antiretrovirals during the third trimester of pregnancy reduced the occurrence of SB and LBW compared to no ARV use or ARV therapy for less than 28 days. We should be cautious about interpreting the results of SB and LBW among women who did not receive antiretrovirals during pregnancy, since these women may have had less access to antenatal care or may have delivered too early to have the opportunity to receive ARV therapy.

Our study indicates that hospitalization during pregnancy is associated with having one or more adverse pregnancy outcomes, particularly PT and LBW. Hospitalizations during pregnancy among HIV infected individuals are mostly caused by acute infections and hypertensive conditions. Infections from the genitourinary tract, lung or gastrointestinal tract have been implicated in the occurrence of preterm delivery.(27) The mechanism by which these infections can promote preterm labor is thought to involve an acute inflammatory response. These conditions require early diagnosis and aggressive management to improve outcomes. An interesting finding of our study was the association between LRTI and adverse pregnancy outcomes; although it is not impossible to rule out that LRTI might represent a marker of some other condition, it did not appear to simply represent a proxy for tobacco use or low CD4 count during pregnancy in our data. Pneumonia during pregnancy has been associated with LBW and increased risk of preterm birth and serious maternal complications, including respiratory failure.(28) The incidence of bacterial pneumonia is higher than in non-HIV-infected populations, and pneumonia can occur at any stage of HIV disease and level of CD4 count. HIV infected persons have an increased incidence of bacteremia and mortality following pneumonia.(29) Pneumonia is frequently caused by Stre*ptococcus pneumoniae*, a pathogen that carries a high burden of disease with enormous costs from treatment, including hospitalizations. (30) Most cases of pneumonia and subsequent hospitalizations could be prevented by increasing coverage of pneumococcal vaccine for HIV infected individuals, as recommended in practice guidelines. (30) Inactivated influenza vaccine should be administered annually to all HIV-infected patients prior to influenza season in order to prevent bacterial pneumonia as a complication of influenza illness. Both of these vaccines are suitable for pregnant women. Also, several therapies may also decrease the risk for bacterial pneumonia, which include ARV use and TMP-SMX use as prophylaxis for PCP when indicated.

Several potentially modifiable factors not directly related to HIV were also identified as increasing the risk of adverse pregnancy outcomes. A history of preterm birth significantly increased the risk of having a preterm birth in subsequent pregnancy, which has been widely reported.(31) While management of women with previous preterm birth is beyond the scope of this discussion, women with such a history should have potential causes evaluated aggressively and be provided with any indicated treatment during subsequent pregnancies. We found that a low BMI (<18.5 kg/m^2) at or near delivery was associated with increased risk of adverse pregnancy outcomes, particularly LBW and SGA. The association between underweight and these outcomes has been previously described in both HIV positive and HIV negative women.(16, 31–34) Women entering pregnancy with a low BMI should be counseled about appropriate weight gain and provided with nutritional supplementation, if needed. Our study also indicated that tobacco use during pregnancy was associated with adverse pregnancy outcomes, even after adjusting for other risk factors. The literature has reported a dose-dependent association between smoking and SGA, PT and SB.(1, 35, 36) Smoking during pregnancy has also been associated with poor adherence to antiretroviral medications and to lower rates of virological suppression.(37, 38) Smoking cessation interventions should be offered to pregnant women who continue to smoke.

We also identified maternal hypertension during pregnancy as a risk factor for adverse pregnancy outcomes. Hypertension during pregnancy may cause fetal growth restriction and increases the risk of pre-eclampsia that could lead to medically indicated interruption of pregnancy and the risk of poor growth and stillbirth.(18, 39, 40) Older age at delivery (> 29 years) in this cohort was associated with the occurrence of SB, which has also been observed among non-HIV infected women.(41, 42) Although the biological mechanism for advanced maternal age increasing the probability of having a SB is unclear, a direct effect of aging on placental function, associated chronic diseases such as hypertension, and medical or obstetric complications are likely contributors.

Conclusion

This study demonstrates a high prevalence of APOs among HIV-infected women. Interventions to reduce risk factors identified in this analysis should be studied for their potential impact on reducing APOs. During pregnancy, underweight women may benefit from nutritional counseling, food or micronutrient supplementation and closer monitoring.

Increasing the coverage of pneumococcal and influenza vaccines in HIV-infected women of child-bearing ages could potentially prevent LRTI and subsequent adverse pregnancy outcomes. Behavior modification for cigarette smoking, drug abuse and alcohol consumption should also be encouraged.

Public health effort should focus on supporting obstetrical and neonatal care for high-risk patients in developing countries, which will not only prevent MTCT of HIV, but also prevent the occurrence of stillbirths, neonatal death and sequelae associated with prematurity.

As more HIV-infected women have intended or unintended pregnancies, additional effort is needed to identify those women at high risk for APOs, which will allow the health support team to provide counseling to those at high risk and intensify support systems that address modifiable risk factors such as smoking, hypertension, lower respiratory tract infections, and low BMI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Prevalence of Adverse Pregnancy Outcomes and 95% Confidence Intervals (CIs) in Study Population

Outcome variables	All births n (Prevalence; 95% CI)	Multiple births n (Prevalence; 95% CI)	Singleton births n (Prevalence; 95% CI)
Live births in study population	n=1533	n=50	n=1483
Preterm delivery	324 (21.1; 19.1 – 23.3)	31 (62.0; 47.2 – 75.4)	293 (19.8; 17.8 – 21.9)
Very preterm delivery	33 (2.2; 1.5 – 3.0)	3 (6.0; 1.3 – 16.6)	30 (2.0; 1.4 – 2.9)
Low birth weight	246 (16.1; 14.3 – 18.0)[1]	36 (72.0; 57.5 – 83.8)	210 (14.2; 12.5 – 16.1)[2]
Very low birth weight	23 (1.5; 0.9 – 2.3)[1]	4 (8.0; 2.2 – 19.2)	19 (1.3; 0.8 – 2.0)[2]
Small for gestational age	204 (13.4; 11.7 – 15.1)[1]	18 (36.0; 22.9 – 50.8)	186 (12.6; 10.9 – 14.4)[2]
Neonatal death	8 (0.5; 0.2 – 1.0)	2 (4.0; 0.5 – 13.7)	6 (0.4; 0.2 – 0.9)
Overall study population	n=1563	n=51	n=1512
Stillbirth	30 (1.9; 1.3 – 2.7)	1 (2.0; 0.05 – 10.5)	29 (1.9; 1.3 – 2.7)
Any adverse pregnancy outcomes	540 (34.5; 32.2 – 37.0)	42 (82.4; 69.1 – 91.6)	498 (32.9; 30.6 – 35.4)

[1] Total population was 1527 for these outcomes due to missing values for birth weight.

[2] Total population was 1477 for these outcomes due to missing values for birth weight.

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Table 2

Risk Factors in the Final Multiple Logistic Regression Models for the Adverse Pregnancy Outcomes*

Risk Factor	PT OR (95% CI)	LBW OR (95% CI)	SGA OR (95% CI)	SB# OR (95% CI)	APOs OR (95% CI)
Age of mother at delivery (years)					
<25				0.95 (0.27 – 3.35)	
25 – 29				1.00	
>29				2.89 (1.05 – 7.90)	
BMI at or near delivery adjusted by GA (kg/m^2)					
Low (<18.5)		2.87 (1.72 – 4.79)	3.25 (2.01 – 5.27)		2.23 (1.43 – 3.46)
Normal (18.5–24.9)		1.00	1.00		1.00
High (≥ 25)		0.60 (0.40 – 0.91)	0.40 (0.26 – 0.64)		0.63 (0.48 – 0.84)
History of previous preterm birth					
Yes	1.92 (1.29 – 2.85)				
No	1.00				
Hospitalization during pregnancy					
Yes	3.56 (2.29 – 5.52)	2.33 (1.27 – 4.26)			3.25 (1.98 – 5.34)
No	1.00	1.00			1.00
Hypertension during pregnancy					
Yes		3.73 (1.96 – 7.10)	2.79 (1.36 – 5.74)		2.72 (1.54 – 4.80)
No		1.00	1.00		1.00
Lower respiratory tract infection (LRTI) during pregnancy					
Yes	2.34 (1.03 – 5.31)			4.13 (1.10 – 15.58)	
No	1.00			1.00	
Most complex ARV regimen received at least 28 days during 3rd trimester					
HAART with PI		0.59 (0.28 – 1.26)		0.14 (0.05 – 0.34)	
HAART w/o PI		0.33 (0.14 – 0.74)		0.11 (0.04 – 0.34)	
Non HAART		0.40 (0.15 – 1.05)			

Risk Factor	PT OR (95% CI)	LBW OR (95% CI)	SGA OR (95% CI)	SB[#] OR (95% CI)	APOs OR (95% CI)
No ARVs or ARVs<28 Days		1.00		1.00	
Receipt of ARVs at conception					
Yes	1.53 (1.11 – 2.09)				1.40 (1.04 – 1.87)
No	1.00				1.00
Plasma HIV-1 RNA concentration at hospital discharge (copied/ml)					
≥ 400	1.47 (1.07 – 2.03)				
<400	1.00				
Reason for receiving ARVs during pregnancy					
Treatment		1.80 (1.26 – 2.56)			
Prophylaxis		1.00			
Tobacco use during pregnancy					
Yes			1.78 (1.24 – 2.54)		1.71 (1.30 – 2.24)
No			1.00		1.00

[*] Since none of the participants that had a SB used a non-HAART regimen during the third trimester, subjects that did not have a SB that used non-HAART during the third trimester were excluded from the model in order to fit this predictor.

[#] Abbreviations: PT for preterm delivery; LBW for low birth weight; SGA for small for gestational age; SB for stillbirth; APOs for adverse pregnancy outcomes; OR for adjusted odds ratio for the other risk factors in the models and CI for confidence interval.