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Repeat Pregnancies Among US Women Living with HIV in the SMARTT Study: Temporal Changes in HIV Disease Status and Predictors of Preterm Birth

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Potential Conflicts of Interest

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Abstract

BACKGROUND—Birth rates among women living with HIV (WLHIV) have increased recently, with many experiencing multiple pregnancies. Yet, viral suppression is often not sustained between pregnancies. Additionally, protease inhibitors (PIs) have been associated with preterm birth, but associations between integrase strand transfer inhibitors (INSTIs) and preterm birth are less well characterized.

METHODS—We studied WLHIV with ≥ 2 liveborn infants enrolled into the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring for ART Toxicities (SMARTT) study between 2007-2018, comparing CD4 counts and viral loads (VLs) between two consecutive SMARTT pregnancies. We evaluated associations of covariates with CD4 and viral suppression, and the association of PI/INSTI use during pregnancy with odds of preterm birth.

RESULTS—There were 736 women who had ≥ 2 liveborn children enrolled in SMARTT (1695 pregnancies). Median CD4 counts remained stable over repeat pregnancies. While > 80% of women achieved VL suppression during pregnancy, more than half had detectable VL early in their subsequent pregnancy. In adjusted models including all singleton pregnancies, an increased odds of preterm birth was observed for women with 1st trimester PI initiation (adjusted odds ratio [OR] 1.97; 95% CI 1.27, 3.07) compared to those not receiving PIs during pregnancy, and for 1st trimester INSTI initiation (adjusted OR 2.39; 95% CI 1.04, 5.46) compared to those never using INSTIs during pregnancy.

CONCLUSIONS—Most WLHIV achieved VL suppression by late pregnancy but many were viremic early in subsequent pregnancies. First trimester initiation of PIs or INSTIs was associated with higher risk of preterm birth.

Summary:

Women living with HIV (WLHIV) often experience multiple pregnancies. Viral suppression following pregnancy in WLHIV is often not maintained. First trimester protease inhibitor and integrase inhibitor initiation was associated with higher risk of preterm birth among women with repeat pregnancies.

Keywords

HIV; pregnancy; preterm birth; antiretrovirals

INTRODUCTION

With advances in HIV treatment, the birth rate among women living with HIV (WLHIV) is increasing¹ with many experiencing multiple pregnancies.² Factors associated with repeat pregnancies among WLHIV include younger age, lower educational attainment, receipt of public assistance, lower viral loads (VLs), higher CD4 counts, and stillbirth or abortion in

the prior pregnancy.^{3,4} Several studies have shown improving HIV disease status over repeat pregnancies. For example, in a multi-country study of WLHIV in Latin America and the Caribbean, the proportion of women with a VL <400 copies/mL increased from 31% at their index pregnancy to 46% at the subsequent pregnancy.⁴ Likewise, Florida et al. showed that the CD4 count early in pregnancy and viral suppression at delivery improved in repeat pregnancies, and was associated with greater ART coverage.⁵ However, specific differences in antiretroviral (ARV) regimens in repeat pregnancies and associations with birth outcomes were not examined.

Protease inhibitor (PI) use in pregnancy is associated with elevated risk of preterm birth, the leading cause of neonatal morbidity and mortality in the United States.⁶⁻⁹ In the Surveillance Monitoring for ART Toxicities (SMARTT) study, we observed a high rate of preterm birth (19%), which was associated with PI-based combination therapy in the first trimester.⁶ Prescribing practices for pregnant WLHIV have changed over time,¹⁰ and little is known about risks associated with integrase strand transfer inhibitors (INSTIs) or newer PIs, or how antiretroviral treatment (ART) switches between pregnancies affect the risk of preterm birth.¹¹

Our objectives were 1) to describe serial changes in CD4 count and VL in repeat pregnancies among WLHIV; 2) to examine associations of maternal characteristics with trends in CD4 count and VL over repeat pregnancies; and 3) to examine associations of PI and INSTI use in pregnancy with preterm birth.

METHODS

Study population and inclusion criteria

We analyzed pregnant WLHIV and their uninfected infants enrolled in the SMARTT study of the Pediatric HIV/AIDS Cohort Study (PHACS), a mixed retrospective and prospective study designed to identify adverse effects of *in utero* ARV exposures in infants and children.^{6,12} For the dynamic cohort, women and their infants were enrolled between 22 weeks of gestation and 1 week after birth.¹³ For the static cohort, pregnant women were generally enrolled in another study during their pregnancy (the Women and Infant Transmission Study [WITS], or the International Maternal Pediatric Adolescent AIDS Clinical Trials [IMPAACT] Protocol 1025 study) and were later enrolled in the SMARTT cohort. Biological mothers living with HIV with two or more SMARTT-enrolled live-birth deliveries through 2018 were eligible for this analysis. All women provided written informed consent for study participation. Women were included in analyses examining CD4 count and VL over repeat pregnancies if they had a CD4 count or VL measure in any study pregnancy. Analyses of associations between PI or INSTI use in pregnancy and preterm birth were conducted among the subset of women with repeat singleton pregnancies and documented ARV use in pregnancy and infant gestational age at birth. The Institutional Review Board at each study site and Harvard T.H. Chan School of Public Health approved the protocol.

Outcome Measures

CD4 and VL measures were obtained through medical chart abstraction. Earliest and latest CD4 count and VL measures in a pregnancy were selected from the interval starting 14 days prior to conception and ending at 7 days after delivery. VL suppression was defined as 400 copies/mL to accommodate this higher limit of detection available in earlier years.

Gestational age was determined according to standard obstetric practice.¹⁴ Preterm birth was defined as birth occurring before 37 completed weeks of gestation.⁹ Medically indicated and spontaneous preterm births were not distinguished, given the importance of all preterm births, the possibility of indication shifting, and the common occurrence of multiple etiologies.

ARV exposure measures and other covariates

PI and INSTI exposures were separately categorized as use at any time during pregnancy (vs non-use) and by timing of initiation (at conception; 1st trimester, defined as 0-13 and 6/7 weeks; 2nd trimester, defined as 14- 27 and 6/7 weeks; and 3rd trimester defined as 28 weeks- 3-day prior to delivery versus no use during pregnancy). Within-woman changes in PI and INSTI use between consecutive pregnancies were examined. For instance, PI use in the index and the subsequent pregnancy could be classified as: (1) a PI-containing regimen in both pregnancies; (2) a non-PI-containing regimen in both pregnancies; or (3) discordant regimens in the two pregnancies. INSTI use was classified similarly.

Covariates of interest for evaluating associations with CD4 and VL over repeat pregnancies included sequence number of the pregnancy while enrolled in SMARTT (e.g. first, second, third, etc.), birth cohort, maternal sociodemographic and health information including sexually transmitted infections (STIs), substance use during pregnancy (tobacco, alcohol, marijuana, or illicit drugs), mode of HIV acquisition (perinatal vs. non-perinatal), and timing of ARV initiation. The birth cohorts were chosen to reflect changes in treatment guidelines in 2011. In evaluating associations of PI/INSTI exposures with preterm birth in repeat singleton pregnancies, maternal sociodemographic information, STIs and substance use were considered as potential confounders of interest.

Statistical Analysis

Sociodemographic characteristics of women and median CD4 count, log₁₀ VL, and viral suppression status for their earliest and latest measures in pregnancy were summarized for up to the first three SMARTT-enrolled pregnancies. Continuous log₁₀ VL measures were analyzed descriptively. We evaluated within-woman changes in CD4 counts and log₁₀VL between the first two consecutive SMARTT pregnancies with available CD4 and VL measures in both pregnancies (defined as the index and the subsequent pregnancy, which may not correspond to the participant's first two SMARTT-enrolled pregnancies). Wilcoxon signed rank tests were used to test for differences in CD4 counts and log₁₀VL between the index and subsequent pregnancy; these comparisons included the earliest measures in the index and subsequent pregnancy, the latest measures in the index and subsequent pregnancy, and the latest measure in the index pregnancy and the earliest measure in the subsequent pregnancy.

Generalized estimating equation (GEE) linear regression models, accounting for within-woman correlation in repeat measures via an exchangeable correlation assumption, were used to evaluate associations of maternal characteristics with earliest and latest CD4 measures across all pregnancies enrolled. A stepwise approach was employed to build multivariable models using a p-value of 0.15 as the criterion to select covariates noted above in the final models. Pregnancy number, birth cohort, and maternal age at delivery were retained in the final model as an *a priori* decision regardless of their statistical significance. We used GEE logistic regression models for the VL suppression outcome (VL < 400 vs. > 400 copies/mL), adjusting for covariates using the same approach described above.

To evaluate associations of PI and INSTI use with preterm birth, we first described preterm birth frequency and ARV exposures (PI and INSTI) over the first three SMARTT-enrolled singleton pregnancies. An exact conditional logistic regression model was used to examine the association of ARV exposure with preterm birth among women receiving discordant ARV regimens (PI-containing vs. non-PI containing regimen; INSTI vs. non-INSTI containing regimen), restricted to the index and subsequent pregnancy. GEE logistic regression models were used to evaluate associations of PI and INSTI exposure with preterm birth across all study pregnancies, adjusting for potential confounders which were selected using the stepwise approach described above. All analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

A total of 2859 biological mothers were enrolled in SMARTT with their children (n=3913) as of July 1, 2018. Among these, 736 women were eligible for our analysis based on having two or more live-birth SMARTT-enrolled pregnancies with CD4 and/or VL measured in any pregnancy. A total of 717 women who had repeat singleton pregnancies (with 1647 pregnancies) and had available information on ARV exposure and preterm birth were included in the preterm birth analysis (See Figure 1S, Supplemental Digital Content).

Of the 736 women with repeat pregnancies, 76% had two pregnancies, 19% three pregnancies, and 5% four or more pregnancies, with a maximum of seven SMARTT-enrolled pregnancies. Maternal characteristics during the first three pregnancies are shown in Table 1. Women with a third pregnancy were more often Black, non-Hispanic, and living with a partner or spouse. Nine percent of the women had acquired HIV perinatally. Only 26% were receiving ARVs at conception of their first pregnancy, compared to 47% and 50% for their second and third pregnancies, respectively. The median inter-pregnancy interval decreased slightly from 26.8 months between the first and second pregnancy to 22.2 months between the second and third pregnancy.

Changes in CD4 Counts over Repeat Pregnancies

The earliest CD4 counts across the first three SMARTT pregnancies were relatively stable, ranging from a median of 453 to 509 cells/mm³ (Figure 1, **panel (a)**). However, there was a small increase in the median earliest CD4 measurement (median gestational age of 9-13

weeks) to the latest CD4 measurement (median gestational age of 34-35 weeks) for all pregnancies, which was most pronounced in the first pregnancy (Figure 1, **panel (a)**). When comparing two consecutive pregnancies with available CD4 data, there was a significant within-woman increase in the earliest CD4 count from the index pregnancy to the earliest CD4 count in the subsequent pregnancy (mean difference 62.9 cells/mm³ [95% CI 31.3, 94.6]). There were no significant within-woman differences in the latest CD4 counts between the index and subsequent pregnancy (mean difference 22.9 cells/mm³ (95% CI -7.4, 53.2)), nor between the latest CD4 count in the index pregnancy and earliest CD4 count in the subsequent pregnancy (mean difference 16.2 cells/mm³ (95% CI -13.8, 46.1)).

Considering all pregnancies, factors independently associated with a lower CD4 count both early and late in pregnancy were birth before 2011 (vs. 2011 or later), annual household income between \$20,000 and \$30,000 (vs. $\geq$ \$30,000), and perinatally-acquired HIV. Receiving ARVs at conception (vs. initiating ARVs in the 2nd/3rd trimester) was associated with a higher earliest and latest CD4 count in pregnancy. Additionally, living with a partner or spouse was associated with a higher latest CD4 count in pregnancy (Table 2).

Changes in VL Suppression over Repeat Pregnancies

In the first pregnancy, only 34% of women had viral suppression at their earliest measurement (median gestational age=13 weeks), with 81% achieving viral suppression at their latest measure in that pregnancy (median gestational age=36 weeks) (Figure 1 (b)). At the beginning of their second pregnancy, 49% had viral suppression, with 82% achieving viral suppression at the latest measure in that pregnancy. The proportion with suppressed VL was lower at the beginning of the second and third pregnancies than at the end of the prior pregnancy. At the end of the third pregnancy, 83% achieved viral suppression (Figure 1).

There was a significant within-woman decrease in both the earliest and latest log₁₀ VL measures between the index and subsequent pregnancy (mean difference: -0.38 log copies/mL (95% CI -0.48, -0.28) and -0.17 log copies/mL (95% CI -0.23, -0.10), respectively). However, from late in the index pregnancy to early in the subsequent pregnancy there was a significant increase in the log₁₀ VL (mean difference 0.63 log copies/mL (95% CI 0.53, 0.72)).

Considering all pregnancies, factors independently associated with higher odds of viral suppression at the earliest measure in pregnancy were delivery year 2011 or later, receiving care at a site in the Northeast region (vs Puerto Rico), more than a high school education, living with a partner or spouse, non-perinatally acquired HIV, not having an STI during pregnancy, and receiving ARVs at conception (vs. initiating ARV in the 2nd/3rd trimester) (Table 3). Likewise, factors independently associated with higher odds of viral suppression at latest measure in pregnancy were lower sequence number of repeat pregnancies, delivery year 2011 or later (vs. < 2004), older age at delivery ($\geq$ 35 years vs. < 25 or 25-30 years), non-Black race, receiving care at a site in the Western US region (vs. Northeast), at least a high school education, household income $\geq$ \$30,000 (vs. $\leq$ \$20,000), non-perinatally acquired HIV, and receiving ARVs at conception (vs. initiating ARV in the 2nd/3rd trimester) (Table 3). Women at research sites in Puerto Rico had decreased odds of viral suppression compared to those in the Northeast region.

ARV Regimens and Preterm Birth over Repeat Singleton Pregnancies

ARV regimens in women changed over time, with an increase in the proportion of women receiving INSTI-containing regimens from their first (3%) to their second (13%) and third (17%) study pregnancies. The most common ARVs included lopinavir/ritonavir, atazanavir, darunavir, nelfinavir, raltegravir, rilpivirine, and nevirapine (See Table 1S, Supplemental Digital Content). For the first three singleton study pregnancies, the frequency of preterm birth was similar for the first two pregnancies (14% and 15%) but increased to 21% in the third pregnancy. The frequency of low birth weight infants (defined as < 2500 grams), was 15%, 12%, and 14% for the first three singleton pregnancies (See Table 2S, Supplemental Digital Content).

In considering only the first two consecutive study pregnancies, 55% of women were on a PI-containing ART regimen in both pregnancies (See Table 3S, Supplemental Digital Content). Comparing these two pregnancies, frequency of preterm birth increased by 3.9% among women remaining on a PI-containing regimen while it decreased by 2.7% and 1.0%, respectively, among women remaining on a non-PI-containing regimen or changing to a non-PI-containing regimen. Twenty-four women received an INSTI in their index pregnancy (12 in the first trimester) and 90 in their subsequent pregnancy (61 in the first trimester) (See Table 3S, Supplemental Digital Content).

After adjusting for the sequence number of all singleton births, birth cohort, household income, and living with a partner, overall PI use during pregnancy was not significantly associated with the risk of preterm birth. However, PI initiation during the first trimester was associated with increased odds of preterm birth compared to women who did not use PIs at any time during pregnancy [OR 1.97 (95% CI 1.27, 3.07), Figure 2]. No such association was observed for receiving a PI regimen at conception or initiating one in the second or third trimester. Similarly, initiating an INSTI-containing regimen in the first trimester was associated with a significant increase in the odds of preterm birth [OR 2.39 (95% CI 1.04, 5.46), Figure 2] compared to not receiving an INSTI-containing regimen during pregnancy.

DISCUSSION

Among WLHIV, CD4 counts early in pregnancy increased with repeat pregnancies. Yet, many were not virally suppressed at their first VL assessment in each pregnancy, even if they achieved viral suppression late in the prior pregnancy, confirming other studies showing viral rebound in the postpartum period.¹⁵⁻¹⁷ This may be due to decreased adherence, barriers to engagement in health care postpartum, and changes in treatment guidelines.^{15,18} The higher rates of viral suppression early in pregnancy in recent calendar years likely reflects changing guidelines. After 2011, WLHIV were more likely to continue ART for their own health following delivery, based on guideline changes in 2011 that recommended ART for all pregnant HIV-infected women regardless of CD4 count.^{10,19}

Identifying barriers to continued engagement in care for WLHIV is essential, as postpartum viral rebound jeopardizes the health of the woman and the health of her family, creating the potential for HIV transmission to a breastfed infant and sexual partners. Several studies have identified challenges WLHIV face in the postpartum period, including balancing infant care

and work, transportation, and stigma that can hinder care engagement and retention.²⁰⁻²³ Utilizing a family-centered care model may optimize continuous care engagement and sustained viral suppression. A recent study of 411 WLHIV in South Africa showed that women randomized to receive integrated pediatric and maternal care after delivery were more likely to be retained in care and maintain viral suppression than those who receive standard of care with pediatric and maternal care provided separately.²⁴ Similarly, a US study demonstrated a 16% increase in the number of women with viral suppression at 6 months postpartum with provision of services through a multidisciplinary perinatal care coordination team, including individualized care plans for WLHIV that address barriers to care and coordination of postpartum care with infant well-child care.²⁵ Novel approaches that support linking maternal and infant treatment may enhance maternal adherence.

About 9% of the women included in this study acquired HIV perinatally. These women had lower mean CD4 counts and were less likely to be virally suppressed, both early and late in pregnancy, than women with non-perinatally acquired HIV. Previous reports from the SMARTT study^{26,27} and others have similarly reported that women with perinatally-acquired HIV have lower baseline CD4 counts at conception and are at greater risk for detectable VL near delivery.^{28,29} These differences in baseline CD4 count may be attributable to suboptimal ART regimens, drug resistance, and/or suboptimal adherence due to psychosocial factors.³⁰

Black women were less likely to have viral suppression compared to non-black women. This may be related to delayed ARV initiation³¹ or other contributing structural factors such as lack of access to HIV care and less social support.^{32,33} Women with less than a high school education were also less likely to be virally suppressed, which may be related to poverty and poor health literacy.^{34,35}

Preterm birth is an important clinical and public health problem, with a higher risk of preterm birth among WLHIV than the general population. In this study, the frequency of preterm birth in women's index and second study pregnancy was 14%, which increased to 21% in their third study pregnancy, compared to an overall preterm birth rate of 19% we previously reported in SMARTT.⁵ This increase in preterm birth in the third pregnancy may be related to increased maternal age or medical conditions such as hypertensive disorders.^{36,37} Further, PI use in the first trimester was significantly associated with increased risk of preterm birth. This is consistent with our previous SMARTT analysis, which showed that PI-based combination regimens in the first trimester were associated with preterm birth.⁶ Surprisingly, we found that PI use at conception was not associated with an increased rate of preterm birth, perhaps due to poor adherence prior to recognition of pregnancy, as evidenced by improvement in viral suppression from early to late in pregnancy. These findings raise important questions about the etiology of preterm birth among WLHIV, which remains unexplained. For example, early PI use may be associated with increased risk of preterm birth due to an alteration of early placentation leading to greater likelihood of placentally-mediated diseases, such as preeclampsia.³⁸⁻⁴⁰ Alternatively, spontaneous preterm birth may be associated with a heightened inflammatory state associated with viremia and/or timing of ART regimen initiation.⁵ Study of women with both indicated and spontaneous preterm birth is essential to understanding these relationships. Importantly, this is the first report of an

association between initiation of an INSTI in the first trimester and an increased odds of preterm birth, compared to those not using INSTIs. However, because only 96 women were exposed to INSTIs in the first trimester, future studies are needed to validate this finding and inform practice guidelines for WLHIV who are either of childbearing potential or are pregnant.

Our study had several limitations. Information on ARV side effects are not collected in SMARTT and self-reported adherence during pregnancy was not collected until 2015. ART regimen complexity including pill burden,⁴¹ pill size, and side effects, as well as social stressors such as stigma and having multiple children can impact adherence.^{17,21} Additionally, the number of women on discordant regimens (PI-containing and non-PI containing) with repeat pregnancies was small, limiting the power to detect differences in preterm birth rate among women who changed regimens between pregnancies as well as limiting the power to detect differences based on timing of initiation. Similarly, the number of women receiving INSTIs was relatively small. It is possible that some women had additional pregnancies (with or without live births) before or between those included in this analysis, resulting in missing obstetric and ART information for these pregnancies. Thus, we did not include prior obstetric history, including preeclampsia or hypertensive disorders of pregnancy and preterm births in the multivariable models; however, these represent important risk factors for preterm birth that should be addressed in future analyses. It is particularly important to define modifiable causes of the higher preterm birth rate among WLHIV. Another limitation is that CD4 and VLs between pregnancies were not collected. Finally, the practice guidelines for ARV treatment of pregnant women have evolved over time. We addressed this by controlling for year of delivery, revealing that viral suppression during pregnancy was more likely after 2010.

In conclusion, in this US cohort, most WLHIV with repeat pregnancies achieved virologic suppression during pregnancy but many had viremia early in their subsequent pregnancy. Maintaining engagement in postpartum care is critical for optimizing women's health and minimizing horizontal and vertical HIV transmission. Further, HIV disease progression between pregnancies was more pronounced among women with perinatally acquired HIV, who had lower CD4 cell counts throughout pregnancy. PI- and INSTI-based regimens initiated in the first trimester were associated with significantly increased odds of preterm birth. Given that US and other guidelines promote some INSTIs as part of a first line regimen in pregnancy, further studies are needed to validate our findings and identify mechanisms for the observed increase in preterm birth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(a)

(b)

Figure 1: Trends in (a) CD4 Counts and (b) Suppressed Viral Load over the First Three SMARTT Pregnancies.

Abbreviations: VL= viral load; IQR= interquartile range; CI= confidence interval

Figure 2: Adjusted Associations of ARV Exposures in Singleton Pregnancy with Preterm Birth Among All Study Pregnancies

Abbreviations: CI= confidence interval; PI= protease inhibitor, INSTI= integrase strand transfer inhibitor; Ref= reference group; ARV= antiretroviral

Adjusted OR: Adjusted Odds Ratio of preterm birth comparing women with vs. without a specific ARV use in pregnancy.

GEE model was fit separately for each ARV exposure, adjusting for number of singleton birth, birth cohort, household income, and living with partner

Table 1.

Maternal Demographic and Health Characteristics for the First Three Study Pregnancies Among 736 Women with Repeat Pregnancies

Characteristic	Study Pregnancy		
	1 st pregnancy (N=736)	2 nd pregnancy (N=736)	3 rd pregnancy (N=177)
Black race	482 (65%)	482 (65%)	134 (76%)
Hispanic	221 (30%)	221 (30%)	44 (25%)
Age at delivery (years)	24.7 (21.4, 29.2)	28.4 (25.0, 33.0)	30.2 (26.9, 34.1)
Inter-pregnancy interval (months) ^a	---	26.8 (13.5, 48.6)	22.2 (9.9, 50.3)
Year of delivery			
< 2004	221 (30%)	89 (12%)	10 (6%)
2004 – 2010	339 (46%)	282 (38%)	62 (35%)
2011 – 2018	176 (24%)	365 (50%)	105 (59%)
Annual household income \$20K	490 (67%)	467 (63%)	114 (64%)
Educational attainment: < High school	251 (34%)	235 (32%)	67 (38%)
Living with partner/spouse	374 (51%)	414 (56%)	111 (63%)
Site region			
Puerto Rico	63 (9%)	63 (9%)	7 (4%)
West	128 (17%)	128 (17%)	33 (19%)
South	274 (37%)	274 (37%)	64 (36%)
Midwest	85 (12%)	85 (12%)	15 (8%)
Northeast	186 (25%)	186 (25%)	58 (33%)
Substance use during pregnancy			
Tobacco	123 (17%)	112 (15%)	26 (15%)
Alcohol	46 (6%)	53 (7%)	12 (7%)
Marijuana	51 (7%)	52 (7%)	12 (7%)
Illicit drugs	61 (8%)	62 (8%)	15 (8%)
Any STIs in pregnancy	305 (41%)	266 (36%)	69 (39%)
Perinatal HIV acquisition	64 (9%)	64 (9%)	14 (8%)
Timing of ARV initiation in pregnancy			
No ARV at any time	17 (2%)	10 (1%)	5 (3%)
On ARV at conception	193 (26%)	343 (47%)	88 (50%)
1st trimester	115 (16%)	143 (19%)	39 (22%)
2nd trimester	308 (42%)	188 (26%)	38 (21%)
3rd trimester	62 (8%)	23 (3%)	3 (2%)
Unknown	41 (6%)	29 (4%)	4 (2%)

Statistics shown are median (IQR) or count (%). ARV=antiretroviral, STI=sexually transmitted infection (trichomonas, gonorrhea, syphilis, chlamydia, HPV, genital warts, genital herpes, bacterial vaginosis), VL=viral load. Illicit drugs included marijuana/hashish, heroin, ecstasy/MDMA, cocaine/crack, methamphetamine, opium, or LSD.

Some measures were not available for the 1st, 2nd, and 3rd pregnancy, including race (50,50,5), ethnicity (2,2,0), household income (74,50,11), education (18,10,2), living arrangement (19,12,2), substance use during pregnancy (37,30,7), STIs (35,21,6), mode of HIV acquisition (18,18,3).

^aInter-pregnancy interval is defined as the number of months between the delivery of one pregnancy and estimated date of conception for the subsequent pregnancy. The interpregnancy interval was only calculated on pregnancies with available gestational age.

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Table 2.

Adjusted Associations of Covariates with CD4 Count for All Pregnancies

Covariates	Earliest CD4 Count (cells/mm ³) in Pregnancy ^a			Latest CD4 Count (cells/mm ³) in Pregnancy ^b		
	Adjusted Mean Difference ^c (95% CI)	P-value ^d	Overall P-value ^e	Adjusted Mean Difference ^c (95% CI)	P-value ^d	Overall P-value ^e
Number of pregnancy	7.17 (-23.7, 38.1)	0.65		7.13 (-32.5, 46.8)	0.72	
Birth cohort						
2011 – 2018	REF	---	<0.001	REF	---	0.01
< 2004	-78.7 (-142, -14.9)	0.02		-50.7 (-116, 15.2)	0.13	
2004 – 2010	-92.7 (-137, -48.1)	<0.001		-73.9 (-121, -26.7)	0.002	
Age (years) at delivery						
35	REF	---	0.98	REF	---	0.88
< 25	-11.3 (-99.4, 76.8)	0.80		15.9 (-69.6, 101)	0.72	
25 - < 30	-14.1 (-98.3, 70.0)	0.74		9.76 (-72.9, 92.4)	0.82	
30 - < 35	-18.0 (-104, 68.2)	0.68		31.9 (-65.5, 129)	0.52	
Annual household income						
\$20K	REF		0.003	REF		< 0.001
> \$20 - 30K	-66.3 (-107, -24.9)	0.002		-68.6 (-107, -29.8)	< 0.001	
> \$30K	23.2 (-35.9, 82.3)	0.44		22.1 (-40.7, 84.8)	0.49	
Unknown	21.0 (-35.2, 77.2)	0.46		39.1 (-17.5, 95.7)	0.18	
Perinatal HIV acquisition	-141 (-228, -55.3)	0.001		-127 (-214, -39.7)	0.004	
Living with partner/spouse	---	---		38.47 (1.11, 75.82)	0.04	
Any STIs in pregnancy	-30.3 (-63.1, 2.54)	0.07		---	---	
Timing of ARV initiation						
2nd/3rd trimester	REF		<0.001	REF		< 0.001
No ARV	-7.36 (-160, 146)	0.92		-112 (-254, 29.7)	0.12	
On ARV at conception	113 (71.2, 155)	<0.001		42.7 (3.76, 81.7)	0.03	
1st trimester	-6.34 (-45.9, 33.2)	0.75		-31.1 (-69.0, 6.76)	0.11	

ARV=antiretroviral, STI=sexually transmitted infection, CI=confidence interval

GEE model was fit separately for earliest and latest CD4 count measured in repeat pregnancies, adjusted for covariates meeting model selection criteria. The adjusted mean difference represents the change in CD4 count per additional pregnancy for sequence number of the pregnancy, or comparing women with a specific characteristic to those without (or in reference level) for other covariates.

^aEarliest CD4 counts in pregnancy, or up to 14 days prior to conception or 7 days after delivery if there was none in pregnancy.

^bLatest CD4 counts in pregnancy, or up to 7 days after delivery or 14 days prior to conception if there was none in pregnancy.

^cAdj. Diff.: Estimated difference in adjusted mean CD4 count as per additional pregnancy for the sequence number of the pregnancy, or comparing women with vs. without a specific characteristic for other covariates.

p -value for testing the effect of each level of a covariate as compared to the reference level.
 p -value for testing the overall effect of a covariate.

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Table 3.

Adjusted Associations of Covariates with Suppressed Viral Load for All Pregnancies

Covariates	Earliest Viral Load in Pregnancy			Latest Viral Load in Pregnancy		
	Adjusted OR (95% CI)	P-value ^a	Overall P-value ^a	Adjusted OR (95% CI)	P-value ^a	Overall P-value ^a
Number of pregnancy	1.07 (0.91, 1.25)	0.44		0.80 (0.65, 0.98)	0.03	
Birth cohort						
2011 - 2018	REF	---	< 0.001	REF	---	< 0.001
< 2004	0.40 (0.26, 0.61)	< 0.001		0.26 (0.16, 0.41)	< 0.001	
2004 - 2010	0.52 (0.40, 0.69)	< 0.001		0.77 (0.53, 1.13)	0.18	
Age (years) at delivery						
35	REF	---	0.03	REF	---	0.01
< 25	0.67 (0.42, 1.05)	0.08		0.38 (0.19, 0.74)	0.005	
25 - < 30	0.87 (0.59, 1.29)	0.49		0.36 (0.19, 0.68)	0.002	
30 - < 35	1.18 (0.81, 1.74)	0.39		0.60 (0.31, 1.16)	0.13	
Black race	---	---		0.62 (0.40, 0.95)	0.03	
Site region						
Northeast	REF	---	0.11	REF	---	< 0.001
Puerto Rico	0.56 (0.32, 0.98)	0.04		0.30 (0.15, 0.58)	< 0.001	
West	1.13 (0.73, 1.74)	0.60		3.83 (1.91, 7.66)	< 0.001	
South	0.77 (0.53, 1.12)	0.17		0.93 (0.62, 1.40)	0.72	
Midwest	0.79 (0.48, 1.30)	0.35		1.04 (0.57, 1.90)	0.90	
Less than high school education	0.67 (0.50, 0.90)	0.01		0.68 (0.49, 0.96)	0.03	
Annual household income						
\$20K	REF	---	0.13	REF	---	0.001
> \$20 - \$30K	0.71 (0.49, 1.03)	0.07		0.85 (0.56, 1.28)	0.43	
> \$30K	0.77 (0.52, 1.14)	0.19		1.91 (1.07, 3.40)	0.03	
Unknown	0.68 (0.40, 1.15)	0.15		2.78 (1.42, 5.44)	0.003	
Living with partner/spouse	1.32 (1.02, 1.71)	0.04				
Perinatal HIV acquisition	0.57 (0.34, 0.94)	0.03		0.32 (0.19, 0.53)	< 0.001	
Any STIs in pregnancy	0.67 (0.52, 0.86)	0.002				
Timing of ARV initiation						
2nd/3rd trimester	REF	---	< 0.001	REF	---	< 0.001
No ARV	3.69 (1.30, 10.48)	0.01		0.28 (0.11, 0.74)	0.01	
On ARV at conception	7.10 (5.34, 9.45)	< 0.001		1.63 (1.15, 2.32)	0.01	
1st trimester	1.79 (1.31, 2.43)	< 0.001		1.30 (0.86, 1.98)	0.22	

ARV=antiretroviral, STI=sexually transmitted infection, CI=confidence interval; OR=odds ratio

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GEE model was fit separately for earliest and latest HIV viral load in repeat pregnancies (with suppression defined as ≥ 400 copies/mL), adjusted for covariates meeting model selection criteria. The adjusted OR represents the odds ratio per additional pregnancy for sequence number of the pregnancy, or comparing women with a specific characteristic to those without (or in reference level) for other covariates.

^aP-value for testing the effect of each level of a covariate as compared to the reference level, or across all levels (overall) for categorical covariates.