Associations between HIV, antiretroviral therapy and preterm birth in the US Women's Interagency HIV Study, 1995–2018: a prospective cohort

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Abstract

Objective: To evaluate the associations of HIV infection with preterm birth (PTB), and of HIV antiretroviral therapy (ART) with PTB.

Methods: We analysed singleton live-born pregnancies among women from 1995 to 2019 in the Women's Interagency HIV Study, a prospective cohort of US women with, or at risk for, HIV. The primary exposures were HIV status and ART use before delivery [none, monotherapy or dual therapy, or highly active antiretroviral therapy (HAART)]. The primary outcome was PTB < 34 weeks, and, secondarily, < 28 and < 37 weeks. We analysed self-reported birth data, and separately modelled the associations between HFV and PTB, and between ART and PTB, among women with HIV. We used modified Poisson regression, and adjusted for age, race, parity, tobacco use and delivery year, and, when modelling the impact of ART, duration from HIV diagnosis to delivery, nadir CD4 count, and pre-pregnancy viral load and CD4 count.

Results: We analysed 488 singleton deliveries (56% exposed to HIV) to 383 women. The risk of PTB < 34 weeks was similar among women with and without HIV, but the risk of PTB < 37 weeks was higher [32% vs. 23%; adjusted risk ratio (aRR) = 1.43; 95% confidence interval (CI): 1.07–1.91] among women with HIV. The risk of PTB < 34 weeks was lower among women with HIV receiving HAART than among those receiving no ART (7% vs. 26%; aRR:0.19; 95% CI: 0.08–0.44). The associations between HAART and PTB < 28 and < 37 weeks were similar.

Conclusions: Antiretroviral therapy exposure was associated with a decreased risk of PTB among a US cohort of women with HIV. Given the growing concerns about ART and adverse pregnancy outcomes, this finding that ART may be protective for PTB is reassuring.

Keywords

INTRODUCTION

Antiretroviral therapy (ART) during pregnancy nearly eliminates the risk of mother-to-child transmission of HIV and improves health and survival for women with HIV [1,2]. Despite over two decades of clinical experience of ART use in pregnancy, the debate about whether ART increases the risk of adverse perinatal outcomes continues due to conflicting data [3,4]. HIV without ART increases the risk of preterm birth (PTB), low infant birthweight (which may also be a proxy for PTB), and stillbirth [5–7]. Recent clinical trials primarily conducted in low- and middle-income countries suggest that ART increases the risk of PTB [8].

Pooled estimates across regional settings suggest that ART may be associated with an increased adjusted odds of PTB (1.32–1.71) [9–14]. This association persists regardless of individual antiretroviral (ARV) drugs prescribed or when ART was started (before vs. during pregnancy) [15–17]. However, not all observational studies have found that ART increases the risk of PTB [10,11,18–21]. It is possible that the observed increased risk noted in low- and middle-income countries may be due in part to inaccurate determination of gestational age at birth because of unknown last menstrual period (LMP) date and lack of access to

prenatal ultrasound dating [22], as well as late entry to prenatal care with initiation of ART in the setting of advanced immunodeficiency [23].

In contrast to low- and middle-income countries, most women with HIV in high-income countries initiate ART before pregnancy, but a recent meta-analysis suggests that women who started ART before conception were at higher risk of PTB compared with those who started after conception [24]. In the US, the PTB rate among women with HIV has declined in the era of increasing ART access [25]. A recent analysis from two US multicentre observational cohorts did not find a higher risk of PTB with ART [13]. However, studies from Europe have identified ART as an independent risk factor for PTB [26–28]. Limitations of prior observational data include lack of a comparison population of women at high risk of HIV who are concurrently at high risk of PTB, small sample size, as well as not adequately addressing natural history of HIV prior to pregnancy in analyses.

We evaluated the associations of HIV with PTB, and ART with PTB in the Women's Interagency HIV Study (WIHS). Given the ongoing debate of the impact of HIV and ART on adverse perinatal outcomes, it remains important to understand these associations in well-characterized longitudinal cohorts of women with, or at risk for, HIV [29].

METHODS

Study setting

The WIHS is an ongoing multicentre, prospective, observational cohort study of women with HIV and socio-demographically matched women without HIV enrolled throughout the US Because we utilized a database of women with or at risk for HIV before, during and after pregnancy, we analysed the self-reported birth data of women with or at risk for HIV, with singleton live-born pregnancies > 20 weeks from 1 October 1995 to 31 March 2019 during WIHS follow-up. No pregnant women with-out HIV were receiving ARV-based pre-exposure prophylaxis (PrEP) nor were any receiving tenofovir for hepatitis B treatment. Women with missing outcomes or those with therapeutic abortion, stillbirth or ectopic pregnancy out-comes were excluded. Participants underwent twice-yearly medical examinations and in-person interviews, as previously described [30]. Women were enrolled following approval by each site's institutional review board. All participants provided written informed consent.

Exposures, outcomes and covariates

The primary exposures were: (1) mother's HIV status at delivery (HIV or no HIV), and (2) ART regimen at the study visit before delivery [none, monotherapy or dual therapy, or highly active antiretroviral therapy (HAART)]. HIV status at enrolment was assessed at the time a woman reported her LMP date. No women without HIV seroconverted during the current study. Highly active ART was defined based on US guidelines as three or more antiretroviral medications, one of which was a protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI), integrase inhibitor (II) or entry inhibitor (EI) [31].

Self-reported PTB < 34 weeks was the primary outcome, with PTB < 28 and < 37 weeks as secondary outcomes. Preterm birth < 34 weeks was selected as the primary out-come

because it is generally used as the cut-off of severe prematurity-associated morbidity and mortality and the gestational age at which obstetrical decisions are often made [32]. Secondary outcomes of PTB < 37 and < 28 weeks are consistent with the World Health Organization definitions for PTB and extreme PTB, respectively [33,34].

Women provided their LMP date and pregnancy out-comes, including month and year of delivery, at each study visit. For women who reported multiple LMP dates during the 300-day interval prior to the delivery date, the LMP date given at the study visit closest to the delivery date was selected. We reviewed follow-up study visits for deliveries between the stated LMP date and the end of the subsequent 300-day time period. As only the month and year of delivery were recorded, we assumed the delivery date to be the middle of the month (i.e. the 15th), and then, in sensitivity analyses, we assumed the delivery date was either the first (i.e. 15 days earlier) or the last day of the month (i.e. 15 days later). Those women with a pregnancy duration < 140 days (20 weeks) or > 300 days (42.8 weeks) between their LMP date and delivery date were removed (listed as 'unable to ascertain gestational age at birth'; Figure 1).

Given that gestational age at birth was calculated as described earlier, we validated this classification scheme using women for whom the exact LMP was available in the clinical chart. Using data from 140 deliveries with dating available in the clinical chart, we found that 89 (64%) had the same gestational age at delivery as the calculated date used in the current study and an additional 23 (16%) were within 1 week. Stated otherwise, 112/140 deliveries (80%) were dated within 1 week using both methods. When pregnancy dating was compared by HIV serostatus, the accuracy of LMP classification did not vary between women with (81%, or 70/86) and without HIV (78%, 42/54). We were unable to confirm whether LMP dating was consistent with early prenatal ultrasound (i.e. best obstetrical estimate).

Directed acyclic graphs were used to identify potential confounders to ensure that these covariates were not on the causal pathway between the exposure (HIV and ART) and the outcome (PTB). Socio-demographic characteristics that may be associated with PTB and ART access included delivery year (1994–2018), maternal age at delivery (continuous), self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Latina, or other including mixed race), parity (0,1 or 2 or more), employed (yes/no), annual non-inflation adjusted household income < ~12 000 (yes/no), and any tobacco use in pregnancy (yes/no). Clinical characteristics that have been previously associated with PTB included pre-pregnancy body mass index (continuous), chronic hypertension (yes/no), pregestational diabetes (yes/no), and antenatal depressive symptoms as defined per a positive screen (yes/no) by the Center for Epidemiologic Studies Depression (CES-D) Scale score   16. HIV-related characteristics included CD4 count (continuous) and plasma viral load suppression (< 50 copies/mL) prior to pregnancy, pre-treatment nadir CD4 count, length of time since HIV diagnosis (years), and time since nadir CD4 count (years). Treatment-related characteristics included timing of ART initiation (started in pregnancy, started before pregnancy), regimen type prior to delivery (Pi-based, NNRTI-based or other) and duration of ART exposure (years).

Statistical analysis

We separately modelled the associations between HIV and PTB, and between ART and PTB, among women with HIV. x^2 and Fisher's exact tests were used to assess group differences for categorical variables, with t-tests used for continuous variables. We used modified Poisson regression models with generalized estimating equations (GEEs) to estimate adjusted risk ratios (aRRs) in order to account for some women delivering more than once during the study period [35]. A directed acyclic graph was used to assess for confounding variables, which graphically depicts posited relationships among exposure, confounders and outcome. We adjusted for socio-demographic characteristics (maternal age at delivery, race/ethnicity, parity, any tobacco use in pregnancy, and year of delivery) in both models, and HIV-related clinical characteristics in the ART/PTB model (duration from HIV diagnosis to delivery, pre-treatment nadir CD4 count, and plasma viral load suppression and CD4 count prior to pregnancy). We used robust standard errors to account for clustering within women who had multiple deliveries. In sensitivity analyses, we assessed the respective impact of potential exposure and outcome misclassification: (1) excluding 18 deliveries to 17 women who started ART > 28 weeks; and (2) defining PTB using two alternative definitions of the delivery date (shifted 15 days forward and backward). To analyse these data, we used SAS (v.9.2; SAS Institute Inc., Cary, NC, USA) for descriptive analyses and STATA (v.MP 15.1; StataCorp, College Station, TX, USA) for GEE models.

RESULTS

Of 4944 assessed women, 3646 (74%) were women with HIV. During the 24-year study period, 912/4944 (18%) women self-reported a pregnancy, resulting in 1893 deliveries (Figure 1). The most common reasons for excluding deliveries from the current analysis were abortion (580/1863 deliveries, 31%), miscarriage (385 deliveries, 21%) and inability to ascertain gestational age at birth (337 deliveries, 18%) (additional less frequent reasons are presented in Figure 1). We compared these 337 deliveries that were excluded due to inability to ascertain gestational age at birth to the final cohort, and both positive HIV status (58% vs. 56%) and, among those with HIV, HAART status (59% vs. 69%) were generally similar. Among those with HIV who were excluded, 33% (63/193) had no visit before their delivery and hence no reported LMP. In the current analysis, we analysed data from 383 women with a singleton live-born pregnancy (to-talling 488 deliveries), including 218 women with HIV (272 deliveries) and 165 without HIV (216 deliveries).

Participant characteristics

Among deliveries to women with HIV, the mean age at delivery was 40 years [standard deviation (SD) = 5.4], 17% were to nulliparous women, 62% were non-Hispanic black, 25% reported tobacco use during pregnancy, and the mean pre-pregnancy body mass index (BMI) was 29 kg/m^2 (SD = 7.8) (Table 1). Comorbid conditions were frequent, including 33% of deliveries affected by chronic hypertension, 31% by antenatal depressive symptoms, and 5% by pregestational diabetes.

Among deliveries to women without HIV, the mean age was 41 years (SD = 5.73), 23% were to nulliparous women, 56% were non-Hispanic black, 29% reported tobacco use during pregnancy, and the mean pre-pregnancy BMI was 31 kg/m^2 (SD = 9.1). Comorbid conditions were also frequent among deliveries to women without HIV. Participant characteristics did not differ significantly between PTB deliveries < 34 weeks and deliveries 34 weeks, regardless of HIV status (Table SI).

Among deliveries to women with HIV, the mean CD4 count prior to delivery was 506 cells/μL (SD = 243) and prior to pregnancy was 541 ceils/μL (SD = 295). Almost half (49%) had a plasma viral load < 50 copies/mL prior to delivery. The pre-treatment nadir CD4 count was 352 cells/μL (SD = 207), of which 21% were < 200 cells/μL. The mean time since HIV diagnosis was nearly 9 years (SD = 4.7) and the time since nadir CD4 count was nearly 5 years (SD = 5.2). None of the above characteristics differed by PTB status (Table S2).

Self-reported ART exposure

A total of 69% of deliveries were exposed to HAART prior to delivery, 14% to monotherapy or dual therapy, and 17% were to women not on ART. Most deliveries to women on HAART (*n* = 188) included a Pi-containing regimen (67%). Among deliveries to women on ART in pregnancy, 64% had started ART before pregnancy. The mean duration of HAART prior to pregnancy was 6 years (SD = 4.05).

Effect of HIV on risk of PTB

The risk of PTB < 34 weeks was similar among women with HIV and those without HIV [10% (27/272) vs. 8% (17/216); aRR = 1.30, 95% Cl: 0.74–2.31] (Table 2). In secondary analysis, the risk of PTB < 37 weeks was higher among women with HIV than among those without HIV (32% vs. 23%, aRR = 1.43, 95% Cl: 1.07–1.91), but not for PTB < 28 weeks.

Effect of ART on risk of PTB among women with HIV

Among deliveries to women with HIV, the risk of PTB < 34 weeks was lower with HAART compared with no ARVs [7% (14/188) vs. 26% (12/47), aRR = 0.19, 95% Cl: 0.08–0.44), as well with as monotherapy or dual therapy [3%, 1/37) compared with no ARVs (aRR = 0.12, 95% Cl: 0.01–0.94) (Table 3). In secondary analysis, the risk of PTB < 37 weeks was lower with HAART than with no ARVs, as well as with mono- or dualtherapy. The risk of PTB < 28 weeks was also lower with HAART.

Most deliveries to women on HAART *(n* = 188) included a PI-containing regimen (67%), and those with a PI regimen were not significantly more likely to have a PTB < 34 weeks compared with those with a non-PI HAART regimen (aRR = 2.61, 95% Cl: 0.65–10.59).

Sensitivity analysis

The results were similar when we excluded deliveries in which ART was initiated after 28 weeks (Tables S3-S4), and when we defined PTB at thresholds of < 34, < 28 and < 37 weeks using the two alternative definitions of the delivery date (shifted 15 days forwards and backwards) (Tables S5-S8).

DISCUSSION

Main findings

In a cohort of women with or at high risk for HIV across the US spanning over two decades, we found that while HIV may be slightly associated with PTB, ART was associated with a decreased risk of PTB. Specifically, both HAART and monotherapy or dual therapy were associated with a > 80% reduction in the likelihood of PTB defined as < 34 weeks, and this result held at thresholds of 28 and < 37 weeks.

Strengths and limitations

There are several limitations. Our ART exposure and PTB outcome were derived based on patient self-report and did not include measures of medication adherence and the best obstetrical estimate or prenatal ultrasound to estimate gestational age at delivery. We were able to confirm that our calculated LMP was consistent with the stated LMP in the clinical chart among a subset of participants. Misclassification of PTB would probably be nondifferential with regard to ART status, biasing our estimates to the null. Second, we were unable to classify the phenotype of PTB (spontaneous vs. medically indicated) as these data were not available, and prior data have suggested that the risk of PTB with ART may vary by subtype of PTB. Third, we were unable to adjust for some important risk factors that may affect a patient's risk of PTB, most importantly a prior history of PTB, as well as receipt of other obstetrical interventions that may affect PTB risk, including supplemental progesterone and cerclage. However, recent data suggest that progesterone supplementation may not prevent recurrent PTB [36]. Given the size of this study, we are unable to assess the relative impact of the individual ARVs used, apart from drug class. Fourth, confounding by indication is an important limitation in any non-randomized study assessing treatment, despite our attempts to adjust for multiple measures of HIV disease severity, comorbidities and socio-economic status in this well-characterized cohort. Fifth, it is likely that the profile of women not on ART has changed during the two decades of this study with changing therapeutic options, HIV-related morbidity and access to prenatal care [37]. While our results may provide prospective, real-world data from across the US, similar to a recent Canadian cohort [38], these data may not be generalizable to current clinical practice given that the majority of deliveries occurred during an earlier era of less potent ART (before 2010). These data may not reflect all pregnant women with HIV, particularly in low- and middle-income countries, because most women in this analysis were of advanced maternal age and suffered from obesity. Notably, these characteristics are increasingly frequent among pregnant women in high-income countries. Finally, a competing risk phenomenon can arise when an early pregnancy loss (i.e. miscarriage or termination) may preclude a consequent PTB from occurring, which may bias results. It is possible that early pregnancy losses could vary by ART exposure status, and may hence affect the apparent number of observed PTB. It should be noted that many clinical trials and observational studies conducted primarily in low- and middle-income countries that found an increased risk of PTB with ART enrolled women in the mid-to-late second trimester given late access to prenatal care. Additionally, the underlying aetiology for an early pregnancy loss is probably different from a later spontaneous or medically indicated PTB. Addressing competing risks can be challenging

due to the need for assumptions and simulation, as well as precise longitudinal data across pregnancy with regard to the timing (i.e. gestational age) of early pregnancy losses [39].

Interpretation

Prior observational data on PTB risk and ART have been conflicting. And while this study may be limited by a relatively small sample size, heterogeneity in treatment regimens and self-report of pregnancy outcomes, it highlights the possibility that ART may prevent PTB in a longitudinal prospective US cohort [40]. These results are largely consistent with a recent analysis of a Canadian cohort of similar sample size ($n = 631$ deliveries) over a similar time period (1997–2018), which showed that women with HIV were at higher risk of spontaneous PTB and that, among those with HIV, ART was associated with a lower risk of spontaneous PTB [38]. A recent meta-analysis of 10 trials consisting of > 6000 women found that ritonavir-boosted lopinavir-containing ART regimens were associated with the highest risk of adverse perinatal outcomes, including PTB [41]. In our data, Pi-containing HAART did not significantly increase the risk of PTB. Two recent randomized controlled trials primarily conducted in sub-Saharan Africa showed that Pi-based ART was associated with a higher risk of PTB [42,43]; however, a Ugandan trial did not find this association [44]. While we did not have data on the phenotype of PTB in the current analysis (i.e. spontaneous vs. medically indicated), it has been suggested that ART is mostly associated with PTB due to medical indications [45]. A recent study from a Spanish cohort found that while HIV infection was associated with both subtypes of PTB, ART was associated with medically indicated PTB [46]. In the current study, most women with HIV on ART were on a PI-containing regimen.

We found that HIV disease severity and treatment characteristics, including duration of HIV infection and treatment, nadir CD4 count and timing of ART initiation, did not differ by PTB status. Previous data have suggested that ART started before conception is associated with an increased risk of PTB [24]. Pre-treatment nadir CD4 count as a measure of immunodeficiency has been shown to be associated with multiple adverse health outcomes outside of pregnancy [47,48].

Possible reasons for why the current study did not find an increased risk of PTB with ART compared with many recent studies include differences in patient characteristics, care provided, dosing differences and residual confounding by other factors across regional settings [37]. An additional factor to consider is that women in the current study were considerably older (mean age 40 years) than in previous studies, which may reflect the increasingly ageing cohort of US pregnant women with HIV [37]. Unlike prior studies which have often included pregnant women who initiated ART during pregnancy or shortly before, we assessed women who had generally been on ART for over 5 years. Women, regardless of HIV status, were at high risk of PTB given the high prevalence (> 25% for each) of chronic hypertension, antenatal depressive symptoms, and tobacco use in pregnancy. In fact, the frequency of PTB < 34 weeks was similar between women without HIV (10%) and with HIV on HAART (7%), both much higher than the current US average (3%) [49]. Nevertheless, these results over a 24-year time period are probably generalizable

to other settings where, as a result of robust HIV testing and treatment programmes, most pregnant women with HIV have been initiated on ART well before getting pregnant.

The exact mechanism by which ART could affect the risk of PTB remains to be defined. Multiple putative paradigms have been proposed to explain why ART increases the risk of PTB, including the profile of placental cytokines, such as decreased interleukin-10, elevated placental leptin levels, heightened foetal recognition by the maternal ART-reconstituted immune system, modulation of placental progesterone production, and ART-mediated placental insufficiency [3]. It has been proposed that inflammation, which is a major risk factor for both spontaneous PTB and PTB due to medical indications, such as pre-eclampsia, is higher in pregnant women with HIV than in those without HIV, possibly explaining their higher risk of PTB [50]. It has been suggested that Pi-based regimens may decrease levels of oestradiol, a hormone critical for the maintenance of a healthy pregnancy [51]. Earlier in the HIV epidemic, ART was reserved for individuals with advanced immunodeficiency. Women in the current study had initiated ART some years before pregnancy and perhaps before immune dysregulation. This may indicate that the adverse effects of ART on pregnancy outcomes noted in some recent studies are driven by their inclusion of women who have recently initiated treatment [4].

In conclusion, we did not observe that ART exposure, including HAART, was associated with a higher risk of PTB among a US cohort of women with HIV. In fact, both ARV exposure and HAART were associated with a decreased risk of PTB, whether defined as < 37 or < 34 weeks. Despite growing concern about ART and adverse pregnancy outcomes, our protective finding between ART and PTB is reassuring but requires further study. Future prospective pregnancy registries of pregnant women with HIV are needed from high-income settings that include standardized obstetrical and HIV outcome data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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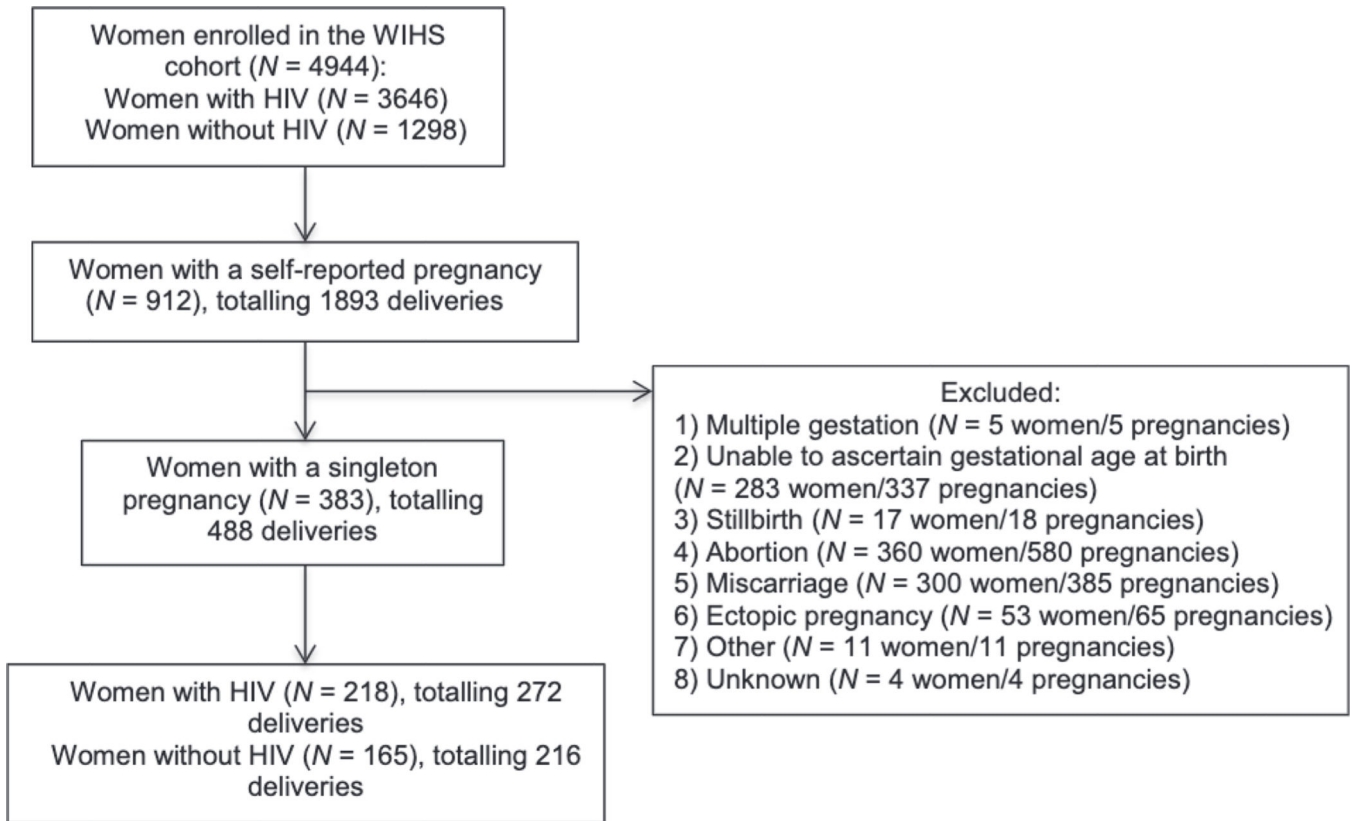**FIGURE 1.**
Flowchart of participants

TABLE 1

Socio-demographic and clinical characteristics of deliveries among women with and without HIV

	Deliveries among women with HIV	Deliveries among women without HIV
	(N = 272)	(N = 216)
Socio-demographic characteristics		
Delivery year [n (%)]		
1994–1998	40 (14.7)	29 (13.4)
1999–2002	56 (20.5)	30 (13.8)
2003–2006	87 (31.9)	65 (30.1)
2007–2010	46 (16.9)	48 (22.2)
2011–2014	28 (10.2)	26 (12.0)
2015–2018	15 (5.5)	18 (8.3)
Maternal age at delivery (years) [mean (SD)]	39.7 (5.37)	40.7 (5.73)
Self-reported race/ethnicity [n (%)]		
Non-Hispanic white	26 (9.5)	20 (9.2)
Non-Hispanic black	169 (62.1)	121 (56.0)
Latina	70 (25.7)	68 (31.4)
Other	7 (2.5)	7 (3.2)
Parity (n = 487) [n (%)]		
0	45 (16.5)	49 (22.7)
1	63 (23.1)	59 (27.4)
2 or more	164 (60.2)	107 (49.7)
Employed [n (%)]	75 (27.5)	86 (39.8)
Annual household income $12 000 (n = 486) [n (%)]	137 (50.5)	95 (44.1)
Tobacco use during pregnancy [n (%)]	68 (25.0)	62 (28.7)
Clinical characteristics		
Pre-pregnancy BMI (kg/m^2) [mean (SD)] (n = 463)	28.9 (7.83)	30.8 (9.08)
Chronic hypertension	90 (33.0)	91 (42.1)
Pregestational diabetes	13 (4.7)	11 (5.0)
Antenatal depressive symptoms [a]	85 (31.2)	63 (29.1)
HIV characteristics		

	Deliveries among women with HIV	Deliveries among women without HIV
	(N = 272)	(N = 216)
CD4 cell count (cells/μL) [mean (SD)]		
Prior to pregnancy (n = 264)	541 (295)	-
Prior to delivery (n = 251)	506 (243)	-
Plasma viral load [n (%)]		
< 50 copies/mL prior to pregnancy (n = 264)	103 (39.0)	-
< 50 copies/mL prior to delivery (n = 249)	122 (49.0)	-
Pre-treatment nadir CD4 cell count		
Cells/(μL (n = 261) [mean (SD)]	352 (207)	-
<200 cells/μL [n (%)]	56 (21.4)	-
Time since nadir CD4 cell count		
Years (n = 270) [mean (SD)]	4.9 (5.22)	-
Duration of HIV infection		
Years (n = 264) [mean (SD)]	8.82 (4.73)	-
ART characteristics		
ART prior to delivery		
No ART	47 (17.2)	-
Monotherapy or dual therapy	37 (13.6)	-
HAART	188 (69.2)	-
Timing of ART initiation among women on ART (n = 225) [n (%)]		
Started in pregnancy	82 (36.4)	-
Started before pregnancy	143 (63.5)	-
Type of HAART (n = 188) [n (%)]		
PI	118 (62.8)	-
PI and NNRTI	8 (4.3)	
NNRTI	45 (23.9)	
Other	17 (9.0)	
HAART started before pregnancy (n = 188)	121 (64.3)	-
Duration of HAART (n = 188)		
Years [mean (SD)]	6.2 (4.05)	-

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Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PTB, preterm birth; SD, standard deviation.

[a]Center for Epidemiologic Studies Depression Scale score ≥ 16.

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TABLE 2

Associations between HIV and preterm birth (PTB)[a]

| | Frequency (%) | | | |
| | Displaying row percentage | | | |
	Yes PTB	No PTB	Risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Primary analysis				
HIV and PTB < 34 weeks				
No HIV	17/216 (7.8)	199/216 (92.1)	1.00	1.00
HIV	27/272 (9.9)	245/272 (90.0)	1.25 (0.71–2.22)	1.30 (0.74–2.31)
Secondary analysis				
HIV and PTB < 28 weeks				
No HIV	6/216 (2.7)	210/216 (97.2)	1.00	1.00
HIV	6/272 (2.2)	266/272 (97.7)	0.79 (0.26–2.41)	0.69 (0.23–2.07)
HIV and PTB < 37 weeks				
No HIV	49/216 (22.6)	167/216 (77.3)	1.00	1.00
HIV	88/272 (32.3)	184/272 (67.6)	1.41 (1.06–1.89) *	1.43 (1.07–1.91) *

Note: N = 488 deliveries (univariate analysis); *N* = 487 (multivariate analysis).

Abbreviations: CI, confidence interval; PTB, preterm birth.

[a] Analysis adjusted for the following covariates: maternal age, race, parity, tobacco use in pregnancy, and delivery year. All models estimated the risk ratio by Poisson regression with robust error variance.

*
$p < 0.05$.

TABLE 3

Associations between antiretroviral therapy (ART) and preterm birth (PTB) among women with HIV[a]

| | Frequency (%) | | | |
| | Displaying row percentage | | | |
	Yes PTB	No PTB	Risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Primary analysis				
ART and PTB < 34 weeks				
No ART	12/47 (25.5)	35/47 (74.4)	1.00	1.00
Monotherapy or dual therapy	1/37 (2.7)	36/37 (97.3)	0.10 (0.01–0.78) *	0.12 (0.01–0.94) *
HAART	14/188 (7.4)	174/188 (92.5)	0.29 (0.14–0.59) *	0.19 (0.08–0.44) *
Secondary analysis				
ART and PTB < 28 weeks				
No ART	4/47 (8.5)	43/47 (91.4)	1.00	1.00
Monotherapy or dual therapy	0/37 (0.0)	37/37 (100.0)	-	-
HAART	2/188 (1.0)	186/188 (98.9)	0.12 (0.02–0.66) *	0.07 (0.01–0.62) *
ART and PTB < 37 weeks				
No ART	23/47 (48.9)	24/47 (51.0)	1.00	1.00
Monotherapy or dual therapy	9/37 (24.3)	28/37 (75.6)	0.50 (0.26–0.93) *	0.57 (0.31–1.03)
HAART	56/188 (29.7)	132/188 (70.2)	0.61 (0.42–0.87) *	0.51 (0.31–0.81) *

Note: $N = 272$ deliveries (univariate analysis); $N = 261$ (multivariate analysis).

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; PTB, preterm birth.

[a] Analysis adjusted for the following covariates: maternal age, race, parity, tobacco use in pregnancy, delivery year, pre-treatment nadir CD4 count (when available), CD4 count before pregnancy, plasma viral load suppression before pregnancy, and duration from HIV diagnosis to delivery. All models estimated the risk ratio by Poisson regression with robust error variance.

*
$p < 0.05$.