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Maternal HIV infection and spontaneous versus provider-initiated preterm birth in an urban Zambian cohort

Joan T PRICE, MD, MPH[1,2,3], **Bellington VWALIKA, MBChB, MSc**[2], **Jessie K EDWARDS, PhD**[4], **Stephen R COLE, PhD**[4], **Margaret P KASARO, MBChB, MSc**[2,3], **Katelyn J RITTENHOUSE, MD**[1], **Andrew KUMWENDA, MBChB**[2], **Mwansa K LUBEYA, MBChB**[1], **Jeffrey S A STRINGER, MD**[3]

[1]Division of Global Women's Health, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2]Department of Obstetrics and Gynaecology, University of Zambia School of Medicine, Lusaka, Zambia

[3]University of North Carolina Global Projects Zambia, Lusaka, Zambia

[4]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

Objective: We investigated the effect of maternal HIV and its treatment on spontaneous and provider-initiated preterm birth (PTB) in an urban African cohort.

Methods: The Zambian Preterm Birth Prevention Study enrolled pregnant women at their first antenatal visit in Lusaka. Participants underwent ultrasound, laboratory testing, and clinical phenotyping of delivery outcomes. Key exposures were maternal HIV serostatus and timing of antiretroviral therapy (ART) initiation. We defined the primary outcome, PTB, as delivery between 16–37 weeks gestational age (GA), and differentiated spontaneous from provider-initiated parturition.

Results: Of 1450 pregnant women enrolled, 350 (24%) had HIV. 1216 (84%) were retained at delivery, 3 of whom delivered <16 weeks. Of 181 (15%) preterm deliveries, 120 (66%) were spontaneous, 56 (31%) were provider-initiated, and 5 (3%) were unclassified. In standardized analyses using inverse probability weighting, maternal HIV increased the risk of spontaneous PTB (RR 1.68; 95% CI 1.12–2.52) but this effect was mitigated on overall PTB (RR 1.31; 95% CI 0.92–1.86) owing to a protective effect against provider-initiated PTB. HIV reduced the risk of preeclampsia (RR 0.32; 95% CI 0.11–0.91), which strongly predicted provider-initiated PTB (RR 17.92; 95% CI 8.13–39.53). The timing of ART start did not affect the relationship between HIV and PTB.

Corresponding author: Joan T. Price, MD, MPH, Division of Global Women's Health, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, 3009 Old Clinic Building, Campus Box 7577, Chapel Hill, NC 27599-7577, Fax: (919) 966-6049, Tel: (919) 962-4717, Joan_Price@med.unc.edu.

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Conclusion: The risk of HIV on spontaneous PTB appears to be opposed by a protective effect of HIV on provider-initiated PTB. These findings support an inflammatory mechanism underlying HIV-related PTB and suggest that published estimates of PTB risk overall underestimate the risk of spontaneous PTB.

Keywords

Preterm birth; HIV; sub-Saharan Africa; preeclampsia; Zambia

INTRODUCTION

Preterm birth (PTB), defined as delivery prior to 37 weeks gestational age (GA), is the leading worldwide cause of child mortality and among the greatest unsolved problems in obstetrics.[1,2] The global burden of PTB is shouldered disproportionately by the developing world, where rates are highest and access to care for premature neonates is often limited.[3]

PTB is not a single disease, but rather a syndrome with many causes that share the final common event of early delivery. There are several validated rubrics available to classify PTB into clinical phenotypes.[4–6] The most basic of these simply differentiates between those early births that arise spontaneously and those that are initiated by a provider. In most settings, spontaneous PTB represents approximately two-thirds of cases and is primarily accompanied by histologic inflammation of the decidua, fetal membranes, and/or umbilical cord.[7] Provider-initiated PTB accounts for approximately one-third of cases, with preeclampsia being the most common reason for early delivery.[8]

Maternal HIV infection complicates 1.5 million pregnancies per year, and increases the risk of PTB by an estimated 1.5-fold (95% confidence interval [CI] 1.24, 1.82).[9] However, maternal HIV is associated with a reduced risk of preeclampsia.[10–14] Treatment of maternal HIV infection with antiretroviral therapy (ART) does not ameliorate PTB risk and in some studies appears to potentiate it, depending upon the specific antiretroviral agent(s) prescribed,[15,16] gestational age dating method,[17] and timing of drug initiation relative to conception.[18–22] We studied the effect of maternal HIV infection and its treatment on the pathologically distinct outcomes of spontaneous PTB and provider-initiated PTB.

METHODS

Study design

The Zambian Preterm Birth Prevention Study (ZAPPS) cohort enrolls women receiving pregnancy care at the Women and Newborn Hospital of the University Teaching Hospitals (WNH-UTH), the primary referral hospital in Lusaka Province, Zambia. The overarching goal of the ZAPPS cohort is to better understand epidemiological and biological determinants of PTB and other adverse outcomes. The cohort was established in collaboration with a consortium of international scientists and research centers under the Global Alliance to Prevent Prematurity and Stillbirth (https://www.gapps.org). The ZAPPS protocol was developed following guidelines for Strengthening The Reporting of Observational Studies in Epidemiology (STROBE).[23]

Study population

Pregnant women meeting the following criteria were eligible for enrollment in the ZAPPS cohort: (1) 18 years of age or older; (2) viable intrauterine singleton or twin pregnancy; (3) presentation to antenatal care prior to 20 weeks GA if HIV-uninfected or 24 weeks GA if living with HIV (to align eligibility with an ongoing randomized trial[24]); (4) residing within Lusaka with no plans to relocate during the study follow-up period; (4) willing to provide written, informed consent; (5) willing to allow participation of their infant(s) in the study; (6) willing to be contacted and followed up at home if necessary.

Research ethics authorities at the University of Zambia School of Medicine reference number: 016-04-14) and the University of North Carolina School of Medicine (study number: 14–2113) each approved the initial ZAPPS protocol and its subsequent revisions. The study also received approval from the Zambian Ministry of Health National Health Research Authority. Participation in all study procedures is voluntary and participants provides written informed consent prior to enrollment.

Study procedures

Full ZAPPS cohort procedures have been presented in detail elsewhere.[25,26] Briefly, pregnant women were recruited from antenatal care clinics of WNH-UTH and neighboring public sector antenatal care clinics. Potential participants underwent an ultrasound examination to determine fetal viability and gestational age by standard biometry measurements.[27,28] Those deemed eligible and interested in study participation then underwent a detailed informed consent procedure in their preferred language: English, Nyanja, or Bemba.

Following the screening and enrollment visit, participants returned for routine antenatal care visits at approximately 24 weeks, 32 weeks, and 36 weeks GA. Study sonographers performed a cervical length evaluation on all participants between 20 and 24 weeks GA, and assessed fetal growth at approximately 32 weeks GA. Study nurses staffed the labour ward at WNH-UTH for 24 hours per day, 7 days per week and collected detailed information about the clinical course and perinatal outcomes of participants and their infants. Approximately 6 weeks following delivery, participants returned to the study clinic for a single postpartum visit. Cohort retention in this analysis was defined as ascertainment of date of delivery at minimum.

Zambia HIV treatment guidelines recommend ART for all pregnant and breastfeeding women infected with HIV. The first-line ART regimen for pregnant women living with HIV in Zambia during this study was tenofovir disoproxil fumarate (TDF), lamivudine or emtricitabine (XTC), and efavirenz (EFV); second-line is zidovudine (ZDV), XTC, plus a protease inhibitor—either lopinavir-ritonavir (LPV-r) or atazanavir-ritonavir (ATV-r).

Data collection

Study nurses collected thorough health and obstetrical history by medical record review and participant interview at enrollment, updating interval information at each subsequent study visit as applicable. Study sonographers performed ultrasound biometry (Sonosite M-Turbo;

Fuji Sonosite, Inc, Bothell, WA) for fetal gestational age estimation on each participant at the time of screening, calculating gestational age by either crown-rump length (if < 14 weeks GA)[27] or head circumference and femur length (if ≥ 14 weeks GA)[28] based on international standards. We tested HIV serostatus for all participants (including those previously diagnosed with HIV or with recent negative test results) at enrollment and again among seronegative participants in the third trimester using the Determine HIV-1/2 Ag/Ab Combo (Abbott Diagnostics, Waltham, MA) and confirmed positive cases with SD Bioline 3.0 (SD Biostandard Diagnostics, India). We categorized timing of ART exposure by medical record review and viral load assay (i.e., HIV-infected women with undetectable viral load at the first visit were assumed to be on preconceptional ART). Viral load was measured with the Abbott RealTime HIV-1 Assay (Abbott Moleculor, Des Plaines, IL). In cases of detectable viral load and unknown ART start date, we tested first-visit plasma samples for drug concentration via liquid chromatography/mass spectrometry.[29–31] In Zambia, CD4 cell count is not routinely measured in pregnancy, but we did document CD4 count among those participants living with HIV who had one performed. At delivery, study nurses assessed neonatal vital status, sex, birthweight (measured twice and averaged on calibrated scales), and parturition classification (spontaneous versus provider-initiated).

Exposures and outcomes

We defined our primary exposure as both a dichotomous variable, characterizing participants as either HIV-infected or -uninfected at the time of enrollment and as a 3-level variable, characterizing participants by HIV status and, for women with HIV, by ART exposure timing (preconceptional or not). Initially seronegative participants who seroconverted during pregnancy (n=5) were categorized as HIV-uninfected. Key covariates included: maternal age, maternal body mass index (BMI; kg/m^2), estimated gestational age at enrollment as determined by fetal ultrasound,[27,28] prior preterm birth (nulliparous, parous with no prior PTB, or parous with 1 or more prior PTB), and preeclampsia (hypertension and at least 2+ proteinuria, with or without attendant eclamptic seizures).

Our primary outcome in this analysis was PTB, defined as delivery between 16 weeks 0 days and 36 weeks 6 days GA. Both liveborn and stillborn infants were included in this primary outcome. PTB was further differentiated as spontaneous (i.e., parturition was initiated without provider intervention) or provider-initiated (i.e., parturition was initated by a provider intervention).

Statistical methods

We described the baseline characteristics of the cohort retained at delivery by calculating median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. We assessed differences in cohort characteristics by HIV and ART timing with univariate tests of association.

We compared the risk, or incidence, of PTB outcomes among our primary exposure categories using inverse probability weighting[32] to account for confounding by maternal age and gestational age at enrollment. Potential confounders were identified using a directed acyclic graph informed by recent literature.[33] We also compared risk of preeclampsia

between women with and without HIV infection at enrollment. We used multiple imputation, the recommended approach over complete-case analysis,[34,35] to account for missing values of age, HIV status, preeclampsia, and PTB parturition classification. Specifically, in each of 100 imputed datasets, we imputed missing values on each of these variables using the fully conditional specification approach,[36] which allows for arbitrary patterns of missingness. We estimated inverse probability weights in each imputed dataset, using logistic regression to estimate the numerator and denominator of the weights; continuous variables were modeled flexibly with restricted quadratic splines.[37] Weights were trimmed such that estimated weights above 10 were set to 10.[32] Within each imputed dataset, inverse probability weights were applied to generalized linear models fit using generalized estimating equations to estimate risk ratios, risk differences, and their robust standard errors. Results were summarized over imputations using Rubin's rule.[38] Technical details are provided in Appendix 1.

Statistical analyses were performed using Stata version 14 (College Station, TX, USA) and SAS version 9.4 (Cary, NC, USA).

RESULTS

Between August 2015 and September 2017, 1450 participants enrolled in ZAPPS, of whom 1097 (76%) were HIV-uninfected at enrollment, 350 (24%) were HIV-infected, and 3 had unknown HIV serostatus (Table 1). HIV-infected participants were older, had fewer years of education, trended towards more alcohol use in pregnancy, had higher parity, enrolled later in gestation, and were more likely to be syphilis seropositive and anemic at baseline (Table 1). Prior PTB, mid-trimester cervical length, and twin gestation were not associated with maternal HIV infection.

Among 350 participants HIV-infected at enrollment, 205 (59%) had initiated ART prior to conception, 99 (28%) had not, and 46 (13%) had unknown ART exposure timing. Of 304 (87%) whose ART regimen was documented by the study, 288 (95%) were taking TDF +XTC+EFV. Viral load was undetectable in 186 (55%) of 340 HIV-infected participants with VL assays recorded. Median CD4 cell count among the 76 with recorded values was 502 cells/mL (IQR 335–717); 4 (5%) had counts < 200 cells/mL.

Through June 2018 (the end of phase I of the cohort), 1216 (84%) participants were retained with a pregnancy outcome recorded. Of these, we excluded 3 with unknown HIV serostatus and 3 who delivered before reaching 16 weeks GA from analyses of outcomes. Of 181 (15%) preterm deliveries, 120 (66%) were spontaneous, 56 (31%) were provider-initiated, and 5 (3%) could not be definitively classified. Among classified preterm deliveries, 42/52 (81%) HIV-infected participants delivered spontaneously compared to 78/124 (63%) HIV-uninfected participants ($\chi 2$ p=0.02). In full cohort analysis using inverse probability weighting, maternal HIV infection increased the risk of spontaneous PTB (RR 1.68; 95% CI 1.12, 2.52) but this effect was mitigated when considering the outcome of overall PTB (RR 1.31; 95% CI 0.92, 1.86) owing to a modest protective effect against provider-initiated PTB (Table 2; Fig. 1). Timing of ART exposure did not modify the effect of HIV on any PTB parturition classification.

Among 765 (63%) participants with at least one blood pressure measurement documented during the delivery hospitalization and, if hypertensive, urinalysis evaluable for proteinuria, 52 (7%) were recorded as preeclamptic, of whom 9 (1%) had eclamptic seizures. In full cohort analysis, participants with HIV infection had lower risk of preeclampsia (RR 0.31; 95% CI 0.11, 0.86) compared to HIV-uninfected participants (Table 3). Preeclampsia increased the risk of overall PTB (RR 4.84; 95% CI 3.37, 6.95) and of provider-initiated PTB (RR 17.92; 95% CI 8.13, 39.53), but did not significantly predict spontaneous PTB (RR 1.34; 95% CI 0.56, 3.19) (Table 4; Fig. 2). Separately from full cohort analyses, we performed a sensitivity analysis in which we assumed all women without definitively documented preeclampsia did not have it and found similar results (Appendix 2).

DISCUSSION

In this well characterized Zambian cohort in which all pregnancies were dated with fetal ultrasound, women living with HIV were at only slightly higher risk of delivering prior to 37 weeks GA than were HIV-uninfected women, an effect that did not reach statistical significance. However, this overall finding appears to belie a more complex story in which HIV exerts opposing effects on spontaneous versus provider-initiated preterm parturition pathways. Our analysis implicates HIV in a near doubling of spontaneous PTB risk while also reducing the risk of preeclampsia by more than 3-fold. Preeclampsia is among the most common reasons for provider-initiated PTB, especially in settings like Zambia where fetal growth is not routinely monitored and preterm delivery for fetal indications is rare. These findings highlight the importance of assigning parturition classification in birth outcomes research while also pointing to an inflammatory mechanism underlying HIV-related PTB.

Preterm birth is not a single, homogeneous outcome but rather a syndrome comprising several distinct disease processes.[4] The simplest phenotypic distinction to make in classifying PTB is whether parturition was spontaneous or was initiated by a medical provider. Further characterization of the phenotypic components of a preterm delivery requires identification and classification of significant concurrent maternal, fetal, and placental factors. While a number of studies in sub-Saharan Africa have demonstrated an increased risk of overall PTB among women with HIV,[9] few have distinguished between spontaneous and provider-initiated deliveries.[39–41] Since HIV appears to promote spontaneous but protect against provider-initiated PTB, published risk estimates of HIV on overall PTB may underestimate the risk of HIV on spontaneous PTB.

A careful classification of PTB is critical to identifying the underlying mechanisms that predispose pregnant women living with HIV to early delivery. Spontaneous preterm labor and delivery, heralded first by regular uterine contractions, spontaneous membrane rupture, or bleeding, is commonly attributed to inflammation with or without clinical or histological evidence of intrauterine infection.[42] Indeed, the inflammatory cytokine milieu of the lower genital tract may be altered by HIV infection,[43] ART exposure,[44] and, along with vaginal dysbiosis, may predict spontaneous PTB.[45,46] In a prior publication from this same ZAPPS cohort, vaginal inflammation in the second trimester was associated with both maternal HIV and with spontaneous PTB.[47] Beyond identifying the common phenotypic pathways to HIV-

associated PTB, understanding the biological mechanisms responsible for potentially modifiable phenotypes will inform development and testing of targeted preventive therapies.

The timing of a woman's exposure to ART relative to conception has been associated with PTB in some analyses, particularly in low-resource settings, but not in others.[18,21,22,48–50] The synthesis of available data is complicated by inconsistent and inaccurate gestational age estimation, confounding by indication for ART use, and selection biases that may exaggerate the effect of preconceptional ART on PTB.[17,51,52] A number of analyses suggest that the association is primarily regimen-dependent,[15,53–55] while others do not.[18,21,56,57] We observed similar risks of spontaneous PTB between women who initiated ART prior to conception and those who did not, but ART exposure in our cohort was almost invariably to TDF-based regimens. The apparent link between ART exposure and spontaneous PTB could benefit from investigation of possible explanatory immune, inflammatory, or hormonal pathways underlying risk.

Our data support other published evidence of a protective effect of maternal HIV infection on preeclampsia.[11,58–60] Data are mixed on the effect of antenatal ART exposure on this risk reduction: some studies show no difference[61,62] or a lower risk[58] of preeclampsia among women living with HIV taking ART compared to uninfected women. Other studies, including a large retrospective cohort from Lusaka, demonstrate an elevated risk of hypertension or preeclampsia among women receiving ART in pregnancy compared to HIV-uninfected women or to those infected but untreated.[10,11,63] Since preeclampsia was infrequent among women living with HIV in the ZAPPS study, we were unable to evaluate the risk of preeclampsia by timing of ART exposure or by ART regimen. The inconsistent findings in the literature may be explained by key population differences in HIV disease severity, ART exposure timing, and ART regimen, or by confounding of underlying risk factors such as obesity, smoking, chronic hypertension, or diabetes.[64] ZAPPS participants had low prevalence of many of these risk factors for preeclampsia, regardless of HIV status. However, it is possible that differential under-reporting or under-diagnosis of these conditions could have biased our findings.

We acknowledge several additional limitations to our analysis. First, we had imperfect cohort retention such that our power to detect risk was reduced, which we addressed using multiple imputation and inverse probability weighting methods. Despite this, we do not know whether women who were missing outcomes differed from those who are not (i.e., whether loss to follow-up was informative). Second, differential estimated gestational age at enrollment between women with and without HIV could have introduced selection bias such that women with HIV enrolled later would have had less opportunity to experience the primary outcome.[65] Indeed, the median gestational age at enrollment was one week later among those with HIV, which we addressed methodologically by reporting standardized results using inverse probability weights. We note that residual bias would tend to underestimate the risk ratio such that our conclusions likely remain valid. Third, significant missingness of our preeclampsia variable, owing to incomplete documentation of blood pressure and/or proteinuria during labor and delivery, is likely to have occurred more frequently among women at lower risk for hypertensive diseases and would thus lead to an over-estimation of the incidence of preeclampsia overall. While we cannot be sure that this

missingness did not bias the associations between HIV and preeclampsia or between preeclampsia and PTB outcomes, we found similar results in a sensitivity analysis that assumed all women without documented preeclampsia did not have it. Finally, CD4 cell count is not routinely collected in pregnant women in Zambia; as such very few women reported a recent result. Whether a causal association exists between PTB and maternal ART exposure timing, duration of HIV diagnosis, viral burden, or CD4 cell count is unknown and should be investigated in future research.

In summary, the present analysis underscores the importance of careful classification of preterm birth in obstetrical HIV research. Women living with HIV in Zambia have an elevated risk of spontaneous preterm birth but a lower risk of provider-initiated preterm birth, owing in part to a lower incidence of preeclampsia than their uninfected counterparts. Studies that combine the phenotypically distinct spontaneous and provider-initiated preterm birth outcomes likely underestimate the risk of HIV on spontaneous preterm birth. A better understanding of the biological and epidemiological mechanisms that associate HIV, preeclampsia, and preterm birth is needed to guide advances in prevention and care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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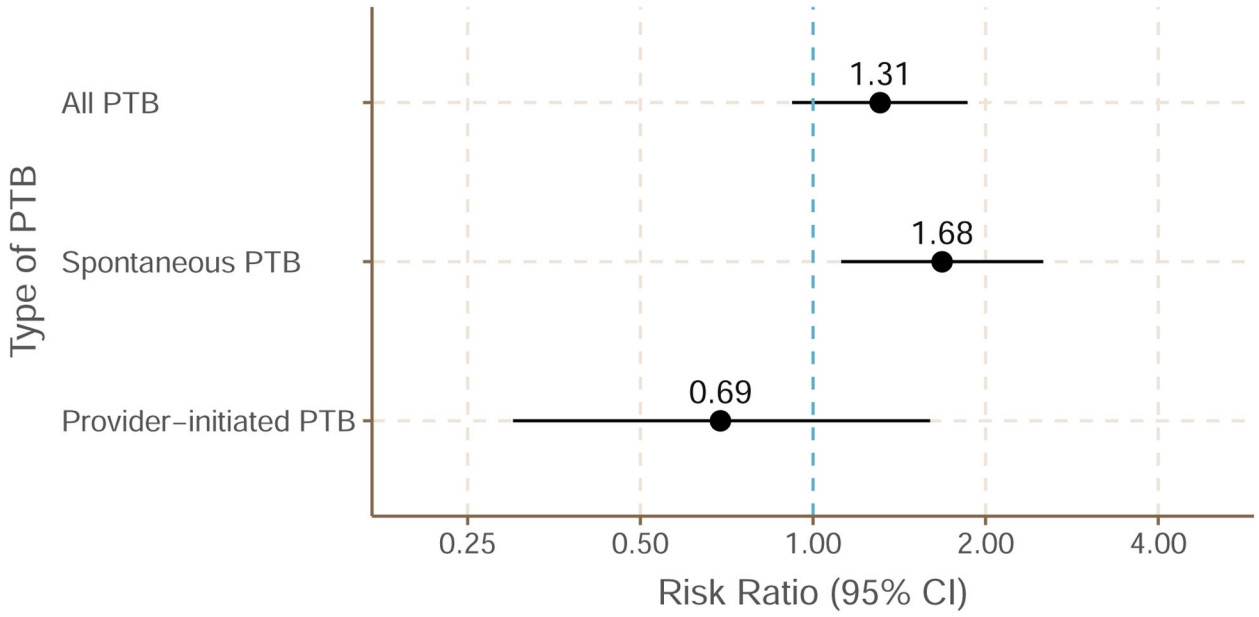

Figure 1.
Risk ratios and 95% confidence intervals for the association between HIV at enrollment and preterm birth, by type of preterm birth (spontaneous or provider-initiated)

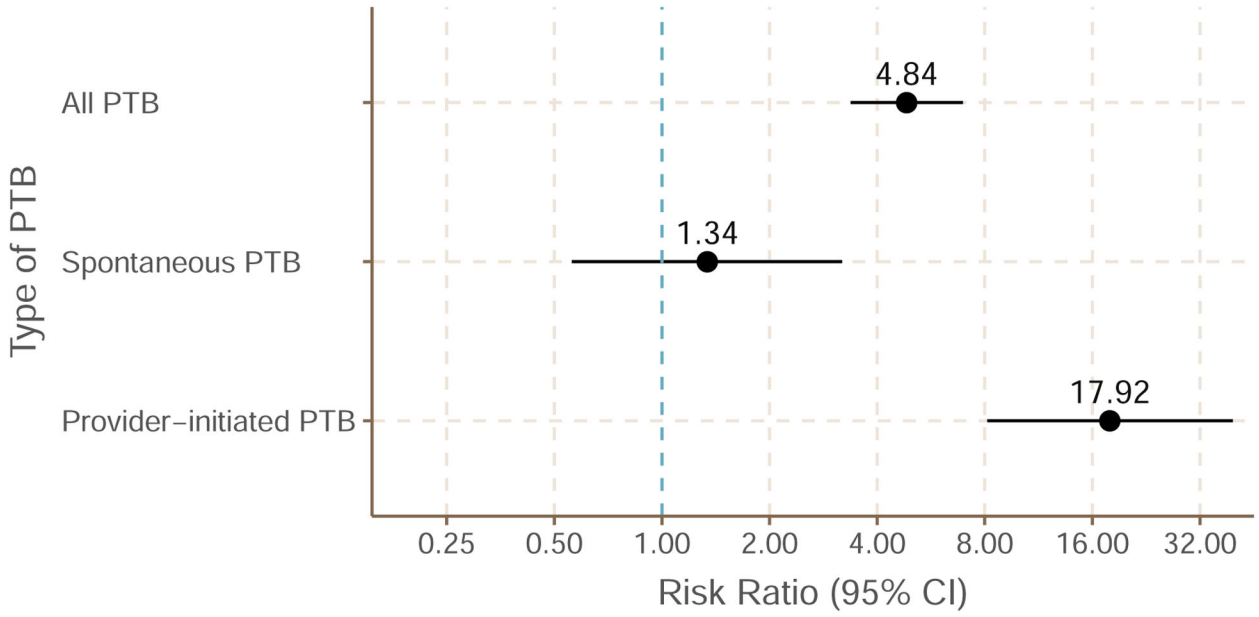

Figure 2.
Risk ratios and 95% confidence intervals for the association between preeclampsia and preterm birth, by type of preterm birth (spontaneous or provider-initiated)

Table 1.

Characteristics of participants by HIV serostatus at enrollment in ZAPPS cohort, August 2015 to September 2017

	HIV− n=1097		HIV+ n=350	
	N	**Value % or median (IQR)**	**N**	**Value % or median (IQR)**
Maternal age, years	1063	26 (23–31)	343	29 (25–33)
<20	98	9.2	13	3.8
20–34	844	79.4	269	78.4
≥35	121	11.4	61	17.8
Maternal education, years	1085	12 (9–12)	347	9 (7–12)
None	18	1.7	8	2.3
0–12 years	907	83.6	315	90.8
≥12 years	160	14.8	24	6.9
Married or cohabiting [*]	908	83.5	292	84.2
Smoking in pregnancy [†]	4	0.4	4	1.2
Alcohol use in pregnancy [‡]	82	7.6	42	12.1
BMI at enrollment, kg/m^2	1032	23.7 (21.2–27.3)	332	23.6 (21.2–27.2)
<18.5	52	5.0	19	5.7
18.5–30.0	830	80.4	271	81.6
>30.0	150	14.5	42	12.7
Parity	1097	1 (0–2)	350	2 (1–3)
Nulliparous	315	34.9	48	15.6
Parous	692	63.1	298	85.1
Prior PTB, n=990				
Parous, no prior PTB	411	59.4	169	56.7
Parous, ≥1 prior PTB	281	40.6	129	43.3
EGA at enrollment, weeks	1097	16 (13–18)	350	17 (14–19)
<14 weeks	337	30.7	89	25.4
Twin gestation	28	2.6	10	2.9
Short cervix < 2.5 cm [§]	29	3.3	6	2.1
Antenatal hypertension [‖]	110	10.1	37	10.6
Hemoglobin at enrollment, g/dL	631	12 (11–13)	220	12 (11–12)
<10.5	82	10.6	58	22.8
Diabetes mellitus [a]	8	0.7	2	0.6
Abnormal UA during antenatal care [b]	162	15.6	62	18.3
Syphilis reactive [c]	34	3.4	36	11.1
ART exposure [d]				

	HIV− n=1097		HIV+ n=350	
	N	Value % or median (IQR)	N	Value % or median (IQR)
Preconceptional	..	..	205	67.4
No preconceptional	..	..	99	32.6
HIV RNA viral copies/μL	..	..	340	0 (0–5100)
<40 (undetectable)	..	..	186	54.7
CD4 cells/mL	..	..	76	502 (335–717)
CD4 <200 cells/mL	..	..	4	5.3

PTB, preterm birth; IQR,interquartile range; BMI, body mass index; EGA,estimated gestational age; ANC,antenatal care; UA,urinalysis; ART,antiretroviral therapy

Table excludes 3 participants with unconfirmed HIV serostatus at enrollment.

[*] Data not available for 10 HIV− and 3 HIV+ participants.

[†] Data not available for 20 HIV− and 4 HIV+ participants.

[‡] Data not available for 21 HIV− and 4 HIV+ participants.

[§] Data not available for 215 HIV− and 60 HIV+ participants.

[//] Defined as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 at enrollment or any follow-up antenatal visit. Data not available for 8 HIV− and 2 HIV+ participants.

[a] Data not available for 19 HIV− and 3 HIV+ participants.

[b] Defined as 1+ leukocyte esterase and/or + nitrites at enrollment or at any follow-up antenatal visit. Data not available for 59 HIV− and 12 HIV+ participants.

[c] Data not available for 81 HIV− and 25 HIV+ participants.

[d] Data not available for 46 HIV+ participants.

Table 2.

Risk of preterm birth, spontaneous preterm birth, and provider-initiated preterm birth between women with and without HIV among 1444 women in the ZAPPS cohort, August 2015 to June 2018, stratified by preconceptional ART use

	N*	No. events†	Risk	Risk difference	95% CI	Risk ratio	95% CI
Crude							
PTB							
HIV −	1095	151	13.8	0	..	1	..
HIV +	349	63	18.0	4.2	−0.7, 9.1	1.30	0.97, 1.74
With preconceptional ART	227	42	18.6	4.8	−1.2, 10.7	1.34	0.95, 1.89
No preconceptional ART	122	20	16.9	3.1	−4.6, 10.8	1.22	0.77, 1.95
Spontaneous PTB							
HIV −	1095	95	8.7	0	..	1	..
HIV +	349	50	14.2	5.5	1.1, 9.9	1.63	1.15, 2.32
With preconceptional ART	227	32	14.1	5.4	0.1, 10.7	1.62	1.07, 2.45
No preconceptional ART	122	17	14.3	5.6	−1.5, 12.7	1.64	0.97, 2.78
Provider-initiated PTB							
HIV −	1095	56	5.1	0	..	1	..
HIV +	349	13	3.8	−1.3	−3.9, 1.3	0.74	0.39, 1.41
With preconceptional ART	227	10	4.5	−0.7	−3.9, 2.6	0.86	0.42, 1.77
No preconceptional ART	122	3	2.6	−2.5	−6.0, 1.0	0.49	0.13, 1.80
Weighted‡							
PTB							
HIV −	1063	148	14.0	0	..	1	..
HIV +	357	65	18.3	4.4	−1.8, 10.5	1.31	0.92, 1.86
With preconceptional ART	230	42	17.9	4.0	−3.7, 11.6	1.28	0.82, 1.98
No preconceptional ART	127	24	19.0	5.1	−4.4, 14.6	1.35	0.81, 2.26
Spontaneous PTB							
HIV −	1063	92	8.7	0	..	1	..
HIV +	357	52	14.6	5.9	0.5, 11.3	1.68	1.12, 2.52
With preconceptional ART	230	33	14.3	5.7	−1.1, 12.5	1.65	1.00, 2.73
No preconceptional ART	127	19	15.0	6.3	−1.7, 14.3	1.72	0.98, 3.02
Provider-initiated PTB							
HIV −	1063	56	5.3	0	..	1	..
HIV +	357	13	3.7	−1.6	−5.0, 1.9	0.69	0.30, 1.60
With preconceptional ART	230	8	3.6	−1.7	−5.6, 2.1	0.64	0.24, 1.70
No preconceptional ART	127	5	4.1	−1.2	−7.0, 4.6	0.72	0.18, 2.96

CI, confidence interval; PTB, preterm birth; ART, antiretroviral therapy

*We observed 1095 HIV− women and 349 HIV+ women, of whom 204 were observed to have preconceptional ART exposure, 99 did not receive preconceptional ART, and 49 were missing information on preconceptional ART. Data exclude 3 participants who miscarried and 3 with unknown HIV serostatus at enrollment.

†Among 908 HIV− women with known gestational age at birth, we observed 128 preterm births (of which, 78 were known to be spontaneous, and 46 were provider-initiated, 4 not classified). Among 303 HIV+ women with known gestational age at birth, we observed 53 preterm births (42 spontaneous, 10 provider-initiated, 1 not classified). Among 181 women on preconceptional ART with known gestational age at delivery, there were 33 preterm births (25 spontaneous, 7 provider-initiated, and 1 not classified); among the 85 HIV+ women not on preconceptional ART, there were 14 preterm births (12 spontaneous and 2 provider-initiated).

‡Standardized using inverse probability weights to account for confounding by age and gestational age at study entry.

Table 3.

Risk of preeclampsia for women with and without HIV, 1444 women in the ZAPPS cohort, August 2015 to June 2018

	N*	No. events	Risk	Risk difference	95% CI	Risk ratio	95% CI
Crude							
HIV −	1097	89	8.1	0	..	1	..
HIV +	350	9	2.7	−5.4	−8.9, −1.9	0.31	0.11, 0.86
Weighted†							
HIV −	1065	87	8.2	0	..	1	..
HIV +	360	10	2.8	−5.4	−9.1, −1.8	0.32	0.11, 0.91

CI, confidence interval

*Prior to imputing, there were 712 participants with preeclampsia and 52 without (680 were missing information on preeclampsia). Among HIV+ women, there were 4 observed events; of those HIV−, there were 48 observed events. Data exclude 3 participants who miscarried and 3 with unknown HIV serostatus at enrollment.

†Standardized using inverse probability weights to account for confounding by age and gestational age at study entry

Table 4.

Risk of preterm birth, spontaneous preterm birth, and provider-initiated preterm birth between women with and without preeclampsia among 1444 women in the ZAPPS cohort, August 2015 to June 2018

	N	No. events	Risk	Risk difference	95% CI	Risk ratio	95% CI
Crude							
PTB *							
No preeclampsia	1347	163	12.1	0	..	1	..
Preeclampsia	97	58	59.6	47.5	31.0, 63.9	4.89	3.43, 6.99
Spontaneous PTB							
No preeclampsia	1347	129	9.6	0	..	1	..
Preeclampsia	97	13	13.3	3.7	−7.3, 14.6	1.32	0.55, 3.14
Provider-initiated PTB							
No preeclampsia	1347	34	2.5	0	..	1	..
Preeclampsia	97	46	46.3	43.8	23.7, 63.9	18.34	8.37, 40.19
Weighted †							
PTB							
No preeclampsia	1347	164	12.2	0	..	1	..
Preeclampsia	96	58	59.1	46.9	30.0, 63.9	4.84	3.37, 6.95
Spontaneous PTB							
No preeclampsia	1347	129	9.6	0	..	1	
Preeclampsia	96	13	13.4	3.8	−7.3, 14.9	1.34	0.56, 3.19
Provider-initiated PTB							
No preeclampsia	1347	35	2.5	0	..	1	
Preeclampsia	96	45	45.7	43.1	22.6, 63.7	17.92	8.13, 39.53

CI, confidence interval; PTB, preterm birth

* Prior to imputing, there were 712 participants with preeclampsia and 52 without (680 were missing information on preeclampsia). Of those observed to have preeclampsia, there were 28 preterm births (6 spontaneous and 22 provider-initiated), and of those without, there were 79 preterm births (57 spontaneous, 21 provider-initiated, and 1 not classified). Data exclude 3 participants who miscarried and 3 with unknown HIV serostatus at enrollment.

† Standardized using inverse probability weights to account for confounding by age and gestational age at study entry