Evaluating the association of prenatal PrEP exposure with perinatal and growth outcomes from infancy through early childhood

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Abstract

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Background

As pre-exposure prophlaxis (PrEP) implementation continues to scale-up among pregnant populations, accruing safety data following prenatal PrEP exposure remains important.

Methods

Data from the PrEP Implementation for Mothers in Antenatal Care study (NCT03070600) was analyzed to evaluate the relationship between prenatal PrEP exposure and birth and infant/child outcomes. Women enrolled during pregnancy at 20 maternal and child health (MCH) clinics in western Kenya and were followed through 9-months postpartum. Those who report swallowing PrEP at any antenatal visits were identified as prenatally PrEP-exposed. In an extension cohort, enrollees and their children were followed through 36 months postpartum. Infant anthropometry

was assessed by trained study nurses. Among a subset, we evaluated prenatal PrEP exposure using tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS).

Results

Overall, 4188 women were included in the analysis, of whom 548 (13.6%) used PrEP during pregnancy, initiating at a median of 26 weeks gestation (IQR 22-30) for a median duration of 11.9 weeks in pregnancy (IQR 7.1-17). Compared to PrEP-unexposed pregnancies, there was no difference in pregnancy loss, stillbirth, preterm birth, or neonatal death among PrEP-exposed pregnancies (all $p>0.55$). There were no differences in infant length or weight at 6-weeks, 6-months, 9-months ($p>0.30$) between children with and without prenatal PrEP exposure, including underweight, stunting, and wasting. Results were similar at 24-months, 30-months and 36-months. We found no differences in adverse perinatal and infant outcomes among Kenyan women with quantifiable prenatal TFV-DP exposure.

Conclusions

We found no significant differences in adverse birth or infant-child outcomes by prenatal PrEP exposure status, including among those confirmed with a biologic measure. These data support findings from prior studies that demonstrate the safety of PrEP use during pregnancy.

Introduction

Incident HIV infections continue to disproportionately occur among cisgender women in Kenya and there is evidence that HIV acquisition risk doubles during pregnancy and the postpartum period compared to non-pregnant periods.[1,2] Acute maternal HIV infection is associated with increased vertical transmission risk,[3] making prevention of HIV among pregnant and breastfeeding cisgender women a global health priority.[4] Based on a large body of safety data from women living with HIV (WLHIV) who used tenofovir disoproxil fumarate (TDF) for HIV treatment during pregnancy and breastfeeding,[5–9] the World Health Organization (WHO) and several national HIV programs, including Kenya, recommend offering daily oral TDF-based pre-exposure prophylaxis (PrEP) to pregnant women at substantial risk for HIV.[5,6,10] Existing safety data of prenatal PrEP use among pregnant women not living with HIV are reassuring, finding no difference in pregnancy loss or preterm birth by PrEP use in pregnancy.[9] However, studies to date have limited follow-up beyond the perinatal period and rely on maternal self-report of PrEP adherence which may not accurately measure infant PrEP exposure.[11,12] Evaluating safety outcomes beyond infancy, following confirmed maternal PrEP exposure could help complete the safety profile for PrEP use during pregnancy.[13]

While many studies support the safety of TDF use during pregnancy[14–16], prenatal TDF exposure among children with HIV-exposure who do not acquire HIV infection (HEU) has been associated with lower length-for-age z-scores compared to those without TDF at 1 year, although this difference may not be clinically significant.[17,18] Studies remain mixed regarding the impact ARV exposure may have on child growth and development, therefore m ARV-exposed children through early childhood is warranted.[14]

We prospectively analyzed data from cisgender women and their infants enrolled in the PrEP Implementation for Mothers in Antenatal Care (PrIMA) study to evaluate the relationship between prenatal PrEP exposure and birth and infant outcomes through 9 months of life. In an extension cohort, we evaluated growth outcomes at 24, 30, and 36 months of life. We also evaluated perinatal and growth outcomes following maternal PrEP use in a subset of women with confirmed tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS). Our overall objective is to expand evidence on the safety of PrEP use during pregnancy in settings with high HIV prevalence.

Methods

Study design and population

We utilized data from the recently completed PrIMA study. PrIMA was a cluster randomized trial of PrEP counseling strategies conducted between January 2018 and July 2021 in 20 mother and child health (MCH) clinics in Homa Bay and Siaya counties, Kenya (NCT03070600). The study protocol has been described in detail previously.[19] Briefly, antenatal care (ANC) attendees were eligible for enrollment if they were: currently pregnant, HIV negative, not currently using PrEP, ≥ 15 years old, tuberculosis negative, planned to reside in the region for at least 1-year postpartum, planned to receive postnatal and infant care at the study facility, and were not currently enrolled in any other studies. Following enrollment, pregnant women were counseled on PrEP as part of routine ANC, either universally (universal arm) or after undergoing HIV risk screening and identified as at risk (targeted arm). Women enrolled at any gestational age during pregnancy and were followed monthly until end of pregnancy and at 6 weeks, 14 weeks, 6 months, and 9 months postpartum, regardless of PrEP use.

Participants were included in the primary analysis if they had complete information on PrEP use and birth outcomes. Those who initiated PrEP postpartum, HIV-seroconverted, had multiple pregnancies, or were missing information on PrEP use in pregnancy/birth outcomes were excluded. We also utilized data collected between October 2020 and February 2023 from an ongoing PrIMA Extension Study (PrIMA-X). The extension cohort was established to evaluate safety outcomes among mother-child pairs enrolled at four PrIMA sites to be followed until the child's 5th birthday with study visits every 6 months. Extension cohort participants were included in the analyses of outcomes beyond 24 months if they had anthropometric data available.

Data collection

At enrollment, demographic, clinical, and psychosocial characteristics were ascertained by trained study staff using tablet-based data capture systems via the REDCap mobile application.[20] Sexual history, behaviors associated with HIV acquisition, and partner HIV status were collected at enrollment and subsequent visits. PrEP was offered at enrollment and available at every follow-up visit. Women who initiated PrEP during the study received PrEP counseling and PrEP refill at all subsequent visits. At follow-up visits, PrEP use and adherence was ascertained via self-report. Pregnancy end date and gestational age at pregnancy end were determined by record abstraction, where available or via direct interview, either at their first postnatal care visit or via telephone call on the expected date of delivery. Birth weight, length, and information on congenital anomalies were collected at the first postnatal visit. Infant weight, height, and head circumference were measured by nurses trained in anthropometry at every postnatal visit.

Laboratory procedures

Dried blood spots (DBS) were collected for TFV-DP quantification by study nurses who received standardized training on DBS collection via fingerstick. DBS were transported to a central -20°C

freezer for storage within 48-hours post-collection. A subset of women who self-reported PrEP use in the prior 30 days at antenatal visits were randomly selected and TFV-DP levels were measured in red blood cells from DBS using validated ultra-performance liquid chromatography-tandem mass spectrometry methods at the University of Colorado.[21,22] Values below the lower limit of quantification for TFV-DP (25 fmol/sample) were considered unquantifiable.[22]

Exposure measures

PrEP exposure was defined as any self-reported PrEP pill-taking during pregnancy. Among the randomly selected subset, confirmed PrEP-exposure during pregnancy was defined as having quantifiable TFV-DP in DBS for exploratory analyses. Those who were randomly selected but did not have detectable TFV-DP were excluded.

Outcomes measures

Perinatal outcomes include gestational age at birth, preterm birth (PTB) (<37 weeks gestation), any congenital malformation (cleft lip, club foot, jointed fingers or toes, extra fingers or toes), pregnancy loss <20 weeks, stillbirth (pregnancy loss ≥20 weeks), and neonatal death (<28 days after birth). Staff underwent standardized multi-day training on conducting anthropometric measurements which included theoretical and didactic sessions and observed practice. WHO weight-for-age, height-for-age, weight-for-height, and small-for-gestational-age z-scores were calculated; underweight, stunting, wasting, and small for gestational age were defined as z-scores <- 2 standard deviations below the mean.[23] Low birth weight (LBW) was defined as <2.5 kg among term infants, and small-for-gestational age (SGA) as below the 10th percentile for birthweight at gestational age at birth. Women who suffered a pregnancy loss or death of a child remained enrolled, allowing for consistent ascertainment of those outcomes.

Statistical analysis

Differences in baseline characteristics by PrEP exposure status were compared using Wilcoxon rank sum and Chi-square tests for continuous and dichotomous measures, respectively. We used generalized estimating equations (GEE) models with clustering by site to evaluate the association of binary birth and infant outcomes by exposure to antenatal PrEP (yes/no); linear regression models were used for continuous birth and infant outcomes. Multivariate models were adjusted for maternal age, gestational age at enrollment, partner HIV status, and maternal syphilis a priori based on their association with adverse perinatal/infant outcomes and/or PrEP uptake in the literature.[6,24,25] PrEP uptake and perinatal/infant outcomes were not associated with randomization arm in the parent study and therefore we did not adjust for randomization arm.[26] In exploratory analyses, frequency of adverse perinatal outcomes were compared between individuals with and without quantifiable TFV-DP levels. All analyses were conducted in Stata 17 (StataCorp, College Station, TX).

Ethical considerations

The PrIMA and PrIMA-X study protocols were approved by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee and University of Washington Human Subjects Division. All participants provided written informed consent.

Results

Population characteristics

Overall, 4188 women met inclusion criteria and were included in the analysis (94% of total PrIMA participants). At enrollment, median maternal age was 24 years (interquartile range [IQR] 21-28)

and median gestational age was 24 weeks (IQR 20-30, Table 1); 25.7% were primigravida. Most (86%) were married or cohabitating with their partner. One-third (34%) reported a partner with unknown HIV status and 3% had partners known to be living with HIV. Median years of education was 8 (IQR 8-12) and 14% had some form of employment. Nearly one in ten women (9.4%) women reported experiencing intimate partner violence (IPV) in the 6 months prior to enrollment, 10% experienced household crowding defined as over three people per room in their residence, and 13% had prior history of a pregnancy loss; 1% reported a previous premature birth.

Self-reported PrEP use during pregnancy

In total, 548 (13.6%) women self-reported PrEP use at some point during pregnancy with a median gestational age of PrEP initiation of 26 weeks gestation (IQR 22-30). Median duration of PrEP use during pregnancy was 11.9 weeks (IQR 7.1-17). Compared to women who did not use PrEP during pregnancy, women who used PrEP were more likely to report having a partner who was known to be living with HIV (19.5% versus 1.5%, p<0.001) or a partner of unknown status (40.9% versus 29.8% p<0.001) (Table 1). Women who used PrEP in pregnancy also more frequently had characteristics associated with HIV acquisition, including engaging in transactional sex, a having recent STI diagnosis, and experiencing IPV in the past 6-months (p<0.001).

Birth outcomes and neonatal death

Frequency of any adverse perinatal outcomes was 25.9% overall (1.2% pregnancy loss < 20 weeks gestation, 3.1% stillbirth, and 18.9% preterm birth, 2.2% small birthweight, 0.5% congenital malformation, not mutually exclusively). There were no differences in the frequency of pregnancy loss (1.3% versus 1.2%, adjusted prevalence ratio (aPR)=1.81, 95% CI: 0.26, 12.35, p=0.545,), stillbirth (3.2% versus 3.1%, aPR=0.77, 95% CI:0.29, 2.07, p=0.607), and preterm birth (16.9% versus 19.2%, aPR=0.95, 95% CI: 0.74-1.21, p=0.675) between woman who did and did not use

PrEP in pregnancy (Table 2). PrEP-exposed and unexposed infants had similar birth weight (3.3 versus 3.4 kg, aPR=-0.04, 95% CI:-0.10-0.03, p=0.276) and birth length (50 cm for both, aPR=-0.62, 95% CI:-0.69-1.93, p=0.337). The proportion of infants who were born SGA was similar among the two groups (10.8% versus 9.8%, aPR=1.10, 95% CI: 0.77-1.56), p=0.602). Few congenital malformations were reported and did not statistically differ between infants who were and were not perinatally exposed to PrEP (0.9% versus 0.5%, aPR=2.23, 95% CI: 0.94, 5.28, p=0.068). There was also no difference in frequency of neonatal deaths between PrEP exposed and unexposed infants (1.8% versus 1.6%, aPR=1.26, 95% CI:0.59-2,72, p=0.73).

Infant growth outcomes through 9-months

Overall, 3,986 infants had complete growth measurements at 6-week, 6-month and 9-months and were included in the infant growth analysis. Median infant weight was similar at 6-weeks (5.0 versus 5.0 kg, aPR=0.01, 95% CI:-0.09.0.10, p=0.897) and 9-months (8.6 versus 8.6 kg, aPR=0.05, 95% CI:-0.06-0.16, p=0.339) between PrEP exposed and unexposed groups; at 6-months, PrEP-exposed infants had slightly higher weight (7.8 versus 7.7 kg, aPR=0.18, 95% CI:0.06-0.29, p=0.004). There were no differences in median infant length at 6-weeks (55.1 versus 55.0 cm, aPR=-0.49, 95% CI:-1.76-0.78, p=0.427), 6-months (66.0 versus 66.0 cm, aPR=0.29, 95% CI:-0.44,1.01, p=0.420), and 9-months (70.5 versus 70.0 cm, aPR=-0.40, 95% CI:-1.77,0.95, p=0.537). Weight-for-age and height-for-age z-scores did not differ by PrEP exposure at any timepoint. Prenatal PrEP exposure was not associated with underweight, stunting, or wasting at any age (Table 3).

Child growth outcomes through 36-months

Overall, 593 mother-child pairs from the PrIMA Extension cohort met inclusion criteria and were included in the extended analysis. Median child age was 25 months (IQR 21-28) at enrollment

into the extension cohort; 16.3% had any PrEP exposure during pregnancy, initiating PrEP at a median of 27 weeks gestation (IQR: 20.4, 30.7) and during pregnancy used PrEP for a median duration of 3.0 months (IQR: 2.0-4.3). Many continued PrEP, with 54% of the 119 women who initiated PrEP during pregnancy continuing to use PrEP through 9-months postpartum. At 24-month visits, there was no difference in mean weight (mean difference -0.07 kg, 95% CI: -0.83-0.69, p=0.783), mean height (mean difference -0.61 cm, 95% CI: -1.85-0.63, p=0.217), frequency of underweight (1.7% vs. 3.3%, aPR=0.51, 95% CI: 0.12-2.16, p=0.361), frequency of stunting (6.0% vs. 10.9%, aPR=0.59, 95%CI: 0.12-2.79, p=0.504) or frequency of wasting (6.0% vs. 7.2%, aPR=0.78, 95%CI: 0.13-4.50, p=0.780) between children with and without prenatal PrEP exposure . Results were similar at 30-month and 36-month visits (Table 4), except at 30-months frequency of wasting was higher among PrEP-exposed (17.3% v 8.9%, aPR=2.07, 95%CI: 1.01, 4.22, p=0.046).

Prenatal PrEP exposure confirmed with TFV-DP quantification

A subset of 103 PrEP initiators were randomly selected for DBS testing and had detectable TFV-DP during pregnancy (18% of all PrEP initiators); these participants were compared to 3505 women who did not use PrEP during pregnancy. Characteristics of this subset were similar to the overall cohort in median maternal age and median gestational age at enrollment, frequency of primigravity, and other characteristics. Compared to PrEP-unexposed women, women with confirmed TFV-DP exposure during pregnancy experienced similar frequencies of stillbirth (3.8% v 3.1%, aPR=1.03, 95% CI: 0.12-8.93, p=0.977), preterm birth (15.5% v 19.2%, aPR=0.92, 95% CI:0.58-1.47, p: 0.729), small-for-gestational-age (13.3% v 9.8%, aPR=1.41, 95% CI:0.78-2.54, p=0.259), and neonatal death (1.0% v 1.6% aPR=0.69, 95% CI:0.09-5.26, p=0.718) (Table 5). At 9 months, there was no association between prenatal PrEP exposure and frequency of underweight (aPR=0.77, 95% CI: 0.23-2.61,p=0.676), stunting (aPR=0.42, 95% CI: 0.06-3.06,

p=0.391), or of wasting (aPR=1.16, 95% CI: 0.39-3.52, p=0.788); results were similar at 6 weeks and 6 months (Table 6).

Discussion

In this large prospective safety evaluation of prenatal PrEP use, maternal PrEP use during pregnancy was not associated with differences in birth or infant outcomes through 9-months of life among Kenyan mother-infant pairs. Similar to prior safety data that relied on self-reported PrEP use, we found no differences in adverse perinatal outcomes among women with prenatal PrEP exposure confirmed with a biologic measure. Retention in the study was high (95%) and in a subset of participants enrolled in an extension cohort, there were also no differences in growth outcomes at 24-, 30- and 36-months among children who did and did not have prenatal PrEP exposure. Our results support prior data indicating safety of prenatal PrEP use and provide evidence for future scale-up of PrEP delivery in this population. To our knowledge, this is the largest study of PrEP use during pregnancy to date with the longest follow-up and the only safety evaluation to include confirmation of maternal PrEP use using quantifiable TFV-DP exposure.

Programmatic PrEP delivery to pregnant women is ongoing in Kenya;[27] however, uncertainty about safety of prenatal PrEP use has hindered PrEP implementation among pregnant women in some HIV high-burden settings. For example, lack of comprehensive safety data delayed PrEP roll-out in South Africa[5,28,29] Currently, most studies contributing data to safety considerations for prenatal PrEP use are from women living with HIV (WLHIV) using TDF as part of combination antiretroviral therapy (ART) regimens for HIV or hepatitis B treatment.[30] Limited data are available on PrEP use throughout pregnancy and the post-partum period, and few studies assess longitudinal outcomes among perinatally exposed infants . In initial PrEP efficacy trials, pregnancy was an exclusion criteria and women who became pregnant during the trials discontinued PrEP

at pregnancy detection. Therefore, these studies only provide data on short-term, early first-trimester exposure, which may not be representative of pregnant individuals at large in these settings. Additionally, studies to date among infants prenatally exposed to PrEP have less than 1 year of follow-up. Prior studies have had smaller sample sizes and often relied on abstracting infant outcomes from medical records which may be incomplete or inaccurate. Expanding on prior studies and evaluating outcomes beyond infancy following maternal PrEP will help complete the safety profile for PrEP use during pregnancy.

Our study found no differences in birth or infant growth outcomes among mother-infant pairs with and without prenatal PrEP exposure. Prior studies on TDF and infant safety outcomes have predominantly come from studies among WLHIV, and thus involve ARV and HIV exposure to infants, rather than purely ARV exposure, which we have examined in this study. In the PROMISE trial, use of TDF-based ART in mothers with HIV resulted in more frequent severe adverse pregnancy outcomes and higher rates of preterm delivery (before 34 weeks) than use of zidovudine-based ART.[35] In the SMARTT cohort, again in WLHIV, TDF use in pregnancy was associated with reduced bone mineral content in neonates compared to exposure to other ARVs, though TFV concentrations in meconium were not associated with infant weight, length or bone mineral content.[18,36] A study using dual-energy X-ray absorptiometry (DXA) suggests that any prenatal antiretroviral (ARV) exposure among infants of WLHIV may lead to decrement in neonatal bone mineral density.[17] It is unclear if these changes are clinically relevant. Importantly, these data from WLHIV are complicated by concomitant ART drugs and HIV disease and may not necessarily reflect safety of PrEP use among HIV-negative mothers. Our findings suggests that prenatal PrEP use is not associated with adverse infant growth among mother-infant pairs who are HIV-negative. WHO guidelines strongly advocate for active surveillance of mother and

infant outcomes during PrEP use in pregnancy and breastfeeding as part of PrEP programs and call for data on longer-term infant outcomes following maternal PrEP use.[28,29,37]

To our knowledge, this is the first study assessing safety of peripartum PrEP exposure utilizing adherence biomarkers. Safety studies of prenatal PrEP use to date have relied on maternal self-report of PrEP adherence[32] which may not accurately measure infant PrEP exposure. Self-reported metrics are subject to recall and social desirability bias and typically overestimates adherence.[38] Self-reported adherence has been shown to correlate poorly with objectively measured adherence in PrEP trials.[39,40]. Biological measures, in contrast, can objectively assess adherence, but are less commonly implemented due to cost and logistical constraints.[41] In a subset of participants with quantified tenofovir exposure from collected specimens, we found no differences in adverse perinatal outcomes among Kenyan women with prenatal PrEP exposure confirmed with a biologic measure.

A limitation of this study is that we relied on last menstrual period (LMP) and fundal height for determining gestational age. LMP and fundal height is standard of care in this setting[42], and prior studies have shown moderate correlation between these measures and ultrasound, depending on gestational age.[43] The study observed relatively low rates of pregnancy loss compared to the underlying population which may indicate selection bias since women in this analysis enrolled at a median of 24 weeks gestation, so earlier pregnancy losses could not have been captured. This gestational age aligns with typical timing of presentation to antenatal care in Kenya.[44,45] Rare outcomes, including congenital anomalies, will require future larger surveillance evaluations. While prevalence of PTB was higher than global estimates, our results align with recent estimates from the region.[46–48] A review on cumulative pregnancy loss prevalence in our study was comparable to current regional and Kenyan estimates[49–51].

Future directions

Understanding the impacts of perinatal PrEP use on infant outcomes is crucial for informing future scale up of PrEP delivery. Additional long-term follow-up of PrEP exposed infants through school-age will be useful to better elucidate the impact of prenatal PrEP exposure on child development. A more comprehensive safety profile including neurodevelopmental assessment and bone density measurements remains important.

Conclusion

In summary, among Kenyan mother-child pairs followed from pregnancy through early childhood, we found no differences in adverse perinatal or growth outcomes between children with and without prenatal PrEP exposure. Our findings suggest that PrEP use during pregnancy does not influence birth and infant outcomes through 36 months postpartum. Our data supports findings from prior studies that demonstrate safety of PrEP use during pregnancy and, importantly, our study contributes to the sparse data available on early childhood outcomes following ARV exposure without the confounder of HIV exposure. In the largest study of PrEP in pregnancy to date, birth, and infant outcomes through 36 months postpartum did not differ by prenatal PrEP exposure, confirmed by adherence biomarkers.

Table 1. Characteristics of women included in birth and infant outcomes analysis by PrEP exposure

	n (%) of Median (IQR)	
Demographic characteristics	**Never PrEP exposed (n=3505)**	**Any PrEP exposure during pregnancy (n=558)**
Age (years)[1]	23.8 (20.8, 28.0)	25.0 (21.0 30.0)
Age category (years) [1]		
<24	2066 (59.0)	276 (49.5)
24-35	1282 (36.6)	240 (43.0)
≥35	155 (4.4)	42 (7.5)
Missing	2	0
Married	2911 (84.0)	481 (87.3)
Missing	40	7
Polygamous[1,2]	313 (10.8)	113 (23.6)
Missing	17	3
Clinical characteristics		
Gestational age at enrollment (weeks) [1]	24.0 (20.0, 30.0)	24.0 (18.6, 28.0)
Missing	0	0
Total attended ANC visits ≥4	2459 (72.9)	411 (76.4)
Missing	133	20
Reactive syphilis[1]	29 (0.8)	13 (2.4)
Missing	58	17
Primigravida[1]	961 (27.5)	89 (16.0)
Missing	15	3
No of living children[1]	1.0 (0.0, 2.0)	2.0 (1.0, 3.0)
Missing	78	9
Prior history of pregnancy loss	438 (12.6)	88 (16.1)
Missing	17	11
Previous premature birth (<37 weeks)[1]	30 (0.9)	12 (2.2)
Missing	0	0
Infant sex (Female)	1560 (51.3)	240 (48.9)
Missing	465	67
Currently breastfeeding at 6 months[3]	2560 (95.4)	371 (94.6)
Missing	158	52
Introduced any other drink or food besides breastmilk yet[4]	1606 (62.9)	255 (68.7)
Missing	7	0
Behavioral risk factors		
No. of lifetime sexual partners[1]	2.0 (2.0, 3.0)	3.0 (2.0, 4.0)
Missing	8	4
HIV status of sexual partner(s) [1]		
Negative	2360 (67.4)	216 (38.9)
Unknown	1043 (29.8)	227 (40.9)
Positive	51 (1.5)	108 (19.5)

No Partner Missing	45 (1.3) 6	4 (0.7) 3
In the last 6 months…		
Engaged in sex in exchange of money/favors[1] Missing	54 (1.5) 14	19 (3.4) 4
Diagnosed with or treated for an STI[1] Missing	72 (2.1) 12	28 (5.1) 4
Forced to have sex[1] Missing	172 (4.9) 11	53 (9.6) 5
Moderate-severe risk for IPV (HITS scale) [1] Missing	222 (6.4) 18	83 (14.9) 2
High risk by NASCOP assessment[1] Missing	384 (11.0) 0	120 (21.5) 0
High risk by empiric HIV risk score[1] Missing	1143 (32.6) 0	354 (63.4) 0
High risk score by either assessment[1] Missing	1334 (38.1) 0	382 (68.5) 0

[1]P-value <0.01 determined by chi-squared test or t-test for categorical and continuous variables, respectively
[2]Among those who are married
[3]Among those who attended their 6-month visit
[4]Among those who attended their 6-month visit and are currently breastfeeding at 6 months

Table 2. Perinatal outcomes by PrEP exposure status

		Median (IQR) or n (%)		Unadjusted GEE regression		Adjusted GEE regression[1]	
		Any PrEP exposure during pregnancy					
	N (n=4063)	No (n=3505)	Yes (n=508)	RR (95% CI)	*P*[1]	RR (95% CI)	*P*[1]
Gestational age at pregnancy end (weeks)	3999	38.0 (37.0, 39.0)	38.0 (37.1, 39.0)	-0.01 (-0.30, 0.29)	0.968	-0.02 (-0.30, 0.27)	0.911
Pre-term birth (<37 weeks gestation)	3999						
No	3244	2783 (80.8)	461 (16.9)	ref		ref	
Yes	755	661 (19.2)	94 (16.9)	0.88 (0.71, 1.10)	0.258	0.95 (0.74, 1.21)	0.675
Pregnancy loss <20 weeks gestation	997						
No	985	831 (98.8)	154 (98.7)	ref		ref	
Yes	12	10 (1.2)	2 (1.3)	1.08 (0.24, 4.89)	0.922	1.81 (0.26, 12.35)	0.545
Stillbirth (≥20 weeks gestation)	997						
No	966	815 (96.9)	151 (96.8)	ref		ref	
Yes	31	26 (3.1)	5 (3.2)	1.04 (0.43, 2.48)	0.935	0.77 (0.29, 2.07)	0.608
Birthweight (kilograms)	2550	3.4 (3.0, 3.6)	3.3 (3.0, 3.6)	-0.02 (-0.08, 0.05)	0.545	-0.04 (-0.10, 0.03)	0.276
Birthweight (<2.5 kilograms)	2550						
No	2494	2110 (97.7)	384 (98.5)	ref		ref	
Yes	56	50 (2.3)	6 (1.5)	0.66 (0.36, 1.22)	0.185	0.68 (0.39, 1.18)	0.171
Small for gestational age	2546						
No	2292	1944 (90.2)	348 (89.2)	ref		ref	
Yes	254	212 (9.8)	42 (10.8)	1.10 (0.78, 1.53)	0.595	1.10 (0.77, 1.56)	0.602
Congenital malformation	3971						
No	3950	3414 (99.5)	536 (99.1)	ref		ref	
Yes	21	16 (0.5)	5 (0.9)	1.98 (0.88, 4.44)	**0.096**	2.23 (0.94, 5.28)	0.068
Neonatal death	3971						
No	3906	3375 (98.4)	531 (98.2)	ref		ref	
Yes	65	55 (1.6)	10 (1.8)	1.15 (0.52, 2.55)	0.725	1.26 (0.59, 2,72)	0.550

[1]Adjusted for maternal age, primigravida, gestational age, partner HIV status, and syphilis status at enrollment

Table 3. Infant growth outcomes at 6-weeks, 6-months, and 9-months postpartum by PrEP exposure

		Median (IQR) or n (%)		Unadjusted GEE regression		Adjusted GEE regression[1]	
		Any PrEP exposure during pregnancy					
	N (n=4063)	No (n=3505)	Yes (n=508)	RR (95% CI)	*P*[1]	RR (95% CI)	*P*[1]
6-Weeks							
Weight (kg)	2476	5.0 (4.5, 5.4)	5.0 (4.5, 5.4)	0.01 (-0.07, 0.09)	0.800	0.01 (-0.09, 0.10)	0.897
Absolute WAZ	2442	0.3 (-0.4, 0.9)	0.3 (-0.4, 0.8)	-0.02 (-0.14, 0.09)	0.656	-0.03 (-0.16, 0.09)	0.576
Underweight (<-2 WAZ)	2442						
No	2370	2086 (97.0)	284 (97.6)	ref		ref	
Yes	72	65 (3.0)	7 (2.4)	0.80 (0.44, 1.45)	0.453	0.84 (0.45, 1.59)	0.597
Height (cm)	2445	55.0 (54.0, 57.0)	55.1 (54.0, 57.0)	-0.50 (-1.68, 0.68)	0.387	-0.49 (-1.76, 0.78)	0.427
Absolute HAZ	2394	-0.2 (-1.1, 0.7)	-0.2 (-0.9, 0.7)	0.5 (-0.15, 0.25)	0.622	0.04 (-0.16, 0.24)	0.679
Stunting (<-2 HAZ)[b]	2394						
No	2164	1907 (90.5)	257 (89.9)	ref		ref	
Yes	230	201 (9.5)	29 (10.1)	1.06 (0.71, 1.59)	0.764	1.20 (0.80, 1.80)	0.367
Absolute WHZ	2350	0.6 (-0.3, 1.7)	0.6 (-0.2, 1.6)	-0.02 (-0.23, 0.18)	0.830	-0.01 (-0.26, 0.23)	0.923
Wasting (<-2 WHZ)	2350						
No	2215	1949 (94.2)	266 (95.0)	ref		ref	
Yes	135	121 (5.8)	14 (5.0)	0.86 (0.44, 1.66)	0.644	0.82 (0.41, 1.62)	0.560
6-Months							
Weight (kg)	2095	7.7 (7.0, 8.5)	7.8 (7.2, 8.7)	0.16 (0.04, 0.29)	.013	0.18 (0.06, 0.29)	0.004
Absolute WAZ	1992	0.1 (-0.7, 0.9)	0.2 (-0.4, 1.1)	0.19 (0.04, 0.34)	**0.016**	0.20 (0.05, 0.35)	**0.013**
Underweight (<-2 WAZ)	1992						
No	1927	1678 (96.6)	249 (97.6)	ref		ref	
Yes	65	59 (3.4)	6 (2.4)	0.69 (0.31, 1.57)	0.378	0.65 (0.28, 1.50)	0.314
Height (cm)	2102	66.0 (64.0, 68.0)	66.0 (64.0, 69.0)	035 (-0.37, 1.07)	0.317	0.29 (-0.44, 1.01)	0.420
Absolute HAZ	1979	-0.3 (-1.1, 0.6)	-0.2 (-1.0, 0.8)	0.07 (-0.14, 0.27)	0.506	0.04 (-0.19, 0.26)	0.733
Stunting (<-2 HAZ)	1979						
No	1808	1575 (91.3)	233 (91.7)	ref		ref	

Yes	171	150 (8.7)	21 (8.3)	0.95 (0.66, 1.37)	0.787	1.04 (0.75, 1.45)	0.813
Absolute WHZ	1960	0.4 (-0.5, 1.4)	0.5 (-0.4, 1.5)	0.11 (-0.08, 0.30)	0.228	0.16 (-0.04, 0.36)	0.117
Wasting (<-2 WHZ)	1960						
No	1886	1645 (96.1)	241 (97.2)	ref		ref	
Yes	74	67 (3.9)	7 (2.8)	0.72 (0.34, 1.54)	0.397	0.66 (0.28, 1.55)	0.336
9-Months							
Weight (kg)	2134	8.6 (7.9, 9.6)	8.6 (8.0, 9.5)	0.03 (-0.08, 0.13)	0.601	0.05 (-0.06, 0.16)	0.339
Absolute WAZ	2014	0.1 (-0.7, 1.0)	0.1 (-0.5, 0.9)	0.04 (-0.06, 0.14)	0.452	0.04 (-0.07, 0.16)	0.444
Underweight (<-2 WAZ)	2014						
No	1939	1671 (96.1)	268 (97.1)	ref		ref	
Yes	75	67 (3.9)	8 (2.9)	0.75 (0.39, 1.46)	0.400	0.75 (0.37, 1.53)	0.436
Height (cm)	2103	70.0 (68.0, 72.0)	70.5 (68.7, 72.0)	-0.28 (-1.64, 1.07)	0.665	-0.40 (-1.77, 0.95)	0.537
Absolute HAZ	1968	-0.4 (-1.3, 0.5)	-0.2 (-1.1, 0.6)	0.10 (-0.14, 0.34)	0.388	0.07 (-0.16, 0.30)	0.556
Stunting (<-2 HAZ)	1968						
No	1793	1544 (90.8)	249 (93.3)	ref		ref	
Yes	175	157 (9.2)	18 (6.7)	0.73 (0.44, 1.21)	0.223	0.81 (0.49, 1.32)	0.396
Absolute WHZ	1958	0.4 (-0.5, 1.3)	0.4 (-0.5, 1.3)	-0.02 (-0.18, 0.14)	0.812	0.03 (-0.15, 0.22)	0.708
Wasting (<-2 WHZ)	1958						
No	1890	1631 (96.5)	259 (97.0)	ref		Ref	
Yes	68	60 (3.5)	8 (3.0)	0.84 (0.43, 1.67)	0.626	0.79 (0.36, 1.70)	0.542

[1]Adjusted for maternal age at enrollment, primigravida at enrollment, gestational age at enrollment, partner HIV status at enrollment, syphilis status at enrollment

Table 4. Early childhood growth outcomes at 24-months, 30-months, and 36-months postpartum by prenatal PrEP exposure

		Median (IQR) or n (%)		Unadjusted GEE regression		Adjusted GEE regression[1]	
		Any PrEP exposure during pregnancy					
	N (n=593)	No (n=482)	Yes (n=111)	RR (95% CI)	*P*[1]	RR (95% CI)	*P*[1]
24-months							
Weight (kg)	340	11.5 (10.5, 12.6)	11.2 (10.1, 12.8)	-0.006 (-0.41, 0.40)	0.964	-0.07 (-0.83, 0.69)	0.783
Absolute WAZ	330	-0.2 (-0.8, 0.6)	-0.2 (-0.9, 0.7)	0.52 (0.09, 2.94)	0.460	0.002 (-0.45, 0.45)	0.989
Underweight (<-2 WAZ)	330						
No	320	263 (96.7)	57 (98.3)	ref		ref	
Yes	10	9 (3.3)	1 (1.7)	-0.54 (-1.67, 0.58)	0.220	0.51 (0.12, 2.16)	0.361
Height (cm)	298	85.0 (83.0, 87.5)	95.0 (92.0, 97.0)			-0.61 (-1.85, 0.63)	0.217
Absolute HAZ	288	-0.4 (-1.2, 0.3)	-0.2 (-0.9, 0.7)	-0.02 (-0.59, 0.55)	0.911	-0.01 (-0.64, 0.62)	0.953
Stunting (<-2 HAZ)	288						
No	259	212 (89.1)	47 (94.0)	ref		ref	
Yes	29	26 (10.9)	3 (6.0)	0.55 (0.11, 2.69)	0.460	0.59 (0.12, 2.79)	0.504
Absolute WHZ	285	0.2 (-0.6, 1.1)	0.6 (-0.2, 1.6)	-0.16 (-1.05, 0.73)	0.606	-0.15 (-1.03, 0.73)	0.623
Wasting (<-2 WHZ)	285						
No	265	218 (92.8)	47 (94.0)	ref		ref	
Yes	20	17 (7.2)	3 (6.0)	0.83 (0.14, 4.93)	0.837	0.78 (0.13, 4.50)	0.780
30-Months							
Weight (kg)	488	12.8 (11.1, 14.0)	12.5 (11.0, 13.6)	-0.21 (-1.38, 0.96)	0.605	-0.22 (-1.27, 0.83)	0.559
Absolute WAZ	473	-0.1 (-1.0, 0.7)	-0.2 (-1.2, 0.3)	-0.17 (-0.80, 0.45)	0.441	-0.16 (-0.72, 0.40)	0.430
Underweight (<-2 WAZ)	473						
No	447	374 (94.7)	73 (93.6)	ref		ref	
Yes	26	21 (5.3)	5 (6.4)	1.21 (0.59, 2.45)	0.605	1.20 (0.70, 2.04)	0.504
Height (cm)	457	89.0 (86.0, 92.0)	89.0 (86.0, 93.0)	-0.04 (-0.76, 0.68)	0.885	-0.03 (0.44, 0.38)	0.835
Absolute HAZ	442	-0.5 (-1.3, 0.4)	-0.3 (-1.2, 0.4)	0.04 (-0.40, 0.48)	0.795	0.07 (-0.33, 0.48)	0.606
Stunting (<-2 HAZ)	442						
No	414	342 (93.2)	72 (96.0)	ref		ref	

Yes	28	25 (6.8)	3 (4.0)	0.59 (0.10, 3.54)	0.561	0.50 (0.10, 2.40)	0.387
Absolute WHZ	436	0.3 (-0.8, 1.1)	0.1 (-1.0, 0.8)	-0.29 (-1.52, 0.94)	0.512	-0.31 (-1.53, 0.92)	0.482
Wasting (<-2 WHZ)	436						
No	391	329 (91.1)	62 (82.7)	ref		Ref	
Yes	45	32 (8.9)	13 (17.3)	1.96 (0.85, 4.48)	0.113	2.07 (1.01, 4.22)	0.046
36-Months							
Weight (kg)	578	14.0 (12.7, 14.9)	14.0 (12.0, 15.0)	0.06 (-0.57, 0.69)	0.789	-0.03 (-0.48, 0.41)	0.821
Absolute WAZ	548	-0.2 (-0.8, 0.4)	-0.2 (-1.1, 0.6)	-0.06 (-0.23, 0.11)	0.351	-0.11 (-0.17, -0.05)	0.01
Underweight (<-2 WAZ)	548						
No	519	427 (94.7)	92 (94.8)	ref		ref	
Yes	29	24 (5.3)	5 (5.2)	0.97 (0.58, 1.61)	0.902	1.07 (0.58, 1.95)	0.833
Height (cm)		94.0 (91.5, 97.0)	95.0 (92.0, 97.0)	0.32 (-0.80, 1.44)	0.430	0.26 (-0.91, 1.43)	0.529
Absolute HAZ	515	-0.2 (-1.0, 0.5)	-0.2 (-1.2, 0.5)	-0.001 (-0.13, 0.13)	0.991	0.01 (-0.05, 0.08)	0.541
Stunting (<-2 HAZ)	515						
No	492	403 (95)	89 (96)	ref		ref	
Yes	23	19 (5)	4 (4)	0.96 (0.50, 1.83)	0.891	0.76 (0.48, 1.20)	0.241
Absolute WHZ	510	0.1 (-0.9, 0.8)	0.1 (-1.1, 0.7)	-0.02 (-0.61, 0.56)	0.905	-0.12 (-0.47, 0.22)	0.342
Wasting (<-2 WHZ)	510						
No	467	384 (92)	83 (91)	ref		ref	
Yes	43	35 (8)	8 (9)	1.05 (0.46, 2.42)	0.904	1.16 (0.57, 2.37)	0.678

[1]Adjusted for maternal age at enrollment, primigravida at enrollment, gestational age at birth, partner HIV status at enrollment, syphilis status at enrollment

Table 5. Perinatal outcomes by confirmed prenatal PrEP exposure

		Median (IQR) or n (%)		Unadjusted GEE regression		Adjusted GEE regression[1]	
		Any detectable DBS during pregnancy					
	N (n=4063)	No (n=3505)	Yes (n=103)	RR (95% CI)	*P*[1]	RR (95% CI)	*P*[1]
Gestational age at pregnancy end	3547	38.0 (37.0, 39.0)	38.0 (38.0, 40.0)	0.35 (0.02, 0.68)	0.041	0.31 (-0.06, 0.68)	0.098
Preterm birth (<37 weeks gestation)	3547						
No	2870	2783 (80.8)	87 (84.5)	ref		ref	
Yes	677	661 (19.2)	16 (15.5)	0.81 (0.51, 1.30)	0.379	0.92 (0.58, 1.47)	0.729
Loss of pregnancy <20 weeks[2]	867						
No	857	831 (98.8)	26 (100)	ref		ref	
Yes	10	10 (1.2)	0 (10)	-	-	-	-
Stillbirth (≥20 weeks gestation)	867						
No	840	815 (96.9)	25 (96.2)	ref		ref	
Yes	27	26 (3.1)	1 (3.8)	1.24 (0.14, 11.36)	0.847	1.03 (0.12, 8.93)	0.977
Birthweight (kilograms)	2235	3.4 (3.0, 3.6)	3.2 (3.0, 3.5)	-0.14 (-0.25, -0.02)	0.024	-0.16 (-0.28, -0.04)	0.012
Birthweight (<2.5 kilograms)[2]	2235						
No	2185	2110 (97.7)	75 (100)	ref		ref	
Yes	50	50 (2.3)	0 (0)	-	-	-	-
Small for gestational age	2231						
No	2009	1944 (90.2)	65 (86.7)	ref		ref	
Yes	222	212 (9.8)	10 (13.3)	1.36 (0.76, 2.43)	0.307	1.41 (0.78, 2.54)	0.259
Congenital malformation[2]	3530						
No	3514	3414 (99.5)	100 (100.0)	ref		ref	
Yes	16	16 (0.5)	0 (0.0)	-	-	-	-
Neonatal death	3530						
No	3474	3375 (98.4)	99 (99.0)	ref		ref	
Yes	56	55 (1.6)	1 (1.0)	0.62 (0.08, 4.63)	0.644	0.69 (0.09, 5.26)	0.718

[1]Adjusted for maternal age, primigravida, gestational age, partner HIV status, and syphilis status at enrollment
[2] PR and P-value not shown due to 0% prevalence among PrEP-exposed

Table 6. Infant growth outcomes at 6-weeks, 6-months, and 9-months postpartum by confirmed PrEP exposure

		Median (IQR) or n (%)		Unadjusted GEE regression		Adjusted GEE regression[1]	
		Any detectable DBS during pregnancy					
	N (n=3608)	No (n=3505)	Yes (n=103)	RR (95% CI)	*P*[1]	RR (95% CI)	*P*[1]
6-Weeks							
Weight (kg)	2242	5.0 (4.5, 5.4)	5.1 (4.5, 5.6)	0.06 (-0.08, 0.20)	0.384	0.03 (-0.13, 0.19)	0.692
Absolute WAZ[a]	2211	0.3 (-0.4, 0.9)	0.4 (-0.4, 1.1)	0.18 (-0.03, 0.38)	0.083	0.13 (-0.09, 0.36)	0.229
Underweight (<-2 WAZ)	2211						
No	2146	2086 (97.0)	60 (100.0)	ref		ref	
Yes	65	65 (3.0)	0 (0.0)	-	-	-	-
Height (cm)	2210	55.0 (54.0, 57.0)	56.0 (54.0, 57.6)	-0.16 (-1.71, 1.39)	0.829	-0.20 (-1.78, 1.37)	0.790
Absolute HAZ	2166	-0.2 (-1.1, 0.7)	0.0 (-0.7, 0.9)	0.35 (-0.003, 0.70)	0.052	0.31 (-0.04, 0.66)	0.081
Stunting (<-2 HAZ)	2166						
No	1960	1907 (90.5)	53 (91.4)	ref		ref	
Yes	206	201 (9.5)	5 (8.6)	0.90 (0.40, 2.07)	0.811	1.15 (0.47, 2.79)	0.762
Absolute WHZ	2127	0.6 (-0.3, 1.7)	0.5 (-0.4, 1.6)	-0.19 (-0.45, 0.07)	0.138	-0.17 (-0.42, 0.07)	0.151
Wasting (<-2 WHZ)	2127						
No	2002	1949 (94.2)	53 (93.0)	ref		ref	
Yes	125	121 (5.8)	4 (7.0)	1.20 (0.47, 3.06)	0.702	1.13 (0.44, 2.93)	0.794
6-Months							
Weight (kg)	1886	7.7 (7.0, 8.5)	7.6 (7.1, 8.5)	0.007 (-0.35, 0.36)	0.968	0.004 (-0.38, 0.39)	0.985
Absolute WAZ	1793	0.1 (-0.7, 0.9)	-0.1 (-0.6, 0.8)	-0.03 (-0.36, 0.30)	0.846	-0.23 (-0.40, 0.35)	0.900
Underweight (<-2 WAZ)	1793						
No	1733	1678 (96.6)	55 (98.2)	ref		ref	
Yes	60	59 (3.4)	1 (1.8)	0.53 (0.09, 3.24)	0.488	0.48 (0.07, 3.22)	0.453
Height (cm)	2102	66.0 (64.0, 68.0)	66.0 (64.0, 68.8)	0.31 (-0.50, 1.12)	0.436	0.20 (-0.79, 1.19)	0.677
Absolute HAZ	1781	-0.3 (-1.1, 0.6)	-0.1 (-1.1, 0.6)	-0.10 (-0.47, 0.28)	0.600	-0.14 (-0.53, 0.25)	0.469
Stunting (<-2 HAZ)	1781						
No	1624	1575 (91.3)	49 (87.5)	ref		ref	

Yes	157	150 (8.7)	7 (12.5)	1.44 (0.66, 3.13)	0.362	1.63 (0.81, 3.27)	0.170
Absolute WHZ	1766	0.4 (-0.5, 1.4)	0.1 (-0.5, 1.3)	-0.03 (-0.33, 0.27)	0.858	0.02 (-0.31, 0.34)	0.912
Wasting (<-2 WHZ)	1960						
No	1699	1645 (96.1)	54 (100.0)	ref		ref	
Yes	67	67 (3.9)	0 (0.0)	-	-	-	-
9-Months							
Weight (kg)	1909	8.6 (7.9, 9.6)	8.6 (7.9, 9.5)	0.05 (-0.24, 0.33)	0.746	0.06 (-0.22, 0.34)	0.642
Absolute WAZ	1801	0.1 (-0.7, 1.0)	-0.1 (-0.5, 0.8)	0.001 (-0.23, 0.23)	0.998	-0.01 (-0.22, 0.20)	0.895
Underweight (<-2 WAZ)	1801						
No	1732	1671 (96.1)	61 (96.8)	ref		ref	
Yes	69	67 (3.9)	2 (3.2)	0.82 (0.39, 1.46)	0.759	0.77 (0.23, 2.61)	0.676
Height (cm)	2103	70.0 (68.0, 72.0)	71.0 (69.0, 72.0)	0.97 (-1.01, 1.94)	0.052	0.70 (-0.45, 1.85)	0.219
Absolute HAZ	1762	-0.4 (-1.2, 0.5)	-0.2 (-1.0, 0.7)	0.16 (-0.17, 0.50)	0.317	0.09 (-0.25, 0.42)	0.598
Stunting (<-2 HAZ)	1762						
No	1603	1544 (90.8)	59 (93.7)	ref		ref	
Yes	159	157 (9.2)	2 (3.3)	0.36 (0.05, 2.55)	0.303	0.42 (0.06, 3.06)	0.391
Absolute WHZ	1752	0.4 (-0.5, 1.3)	0.3 (-0.6, 1.1)	-0.16 (-0.45, 0.13)	0.266	-0.10 (-0.41, 0.21)	0.510
Wasting (<-2 WHZ)	1752						
No	1689	1631 (96.5)	58 (95.1)	ref		ref	
Yes	63	60 (3.5)	3 (4.9)	1.39 (0.50, 3.86)	0.532	1.16 (0.39, 3.52)	0.788

[1]Adjusted for maternal age at enrollment, primigravida at enrollment, gestational age at enrollment, partner HIV status at enrollment, syphilis status at enrollment

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