Exposure to HIV Pre-Exposure Prophylaxis in Pregnancy and Perinatal Outcomes among Women in Western Kenya

Ben Ochieng Odhiambo

A thesis
submitted in partial fulfillment of the requirements for the degree of
Master of Public Health

University of Washington

2024

Committee:

Jillian Pintye

Grace John-Stewart

John Kinuthia

Program Authorized to Offer Degree:

School of Public Health-Global Health

University of Washington

Abstract

Exposure to HIV Pre-Exposure Prophylaxis in Pregnancy and Perinatal Outcomes among Women in Western Kenya

Ben Ochieng Odhiambo

Chair of the Supervisory Committee:

Jillian Pintye
Department of Global Health

Introduction:

While existing safety data on prenatal PrEP use are reassuring, there is a need for continued surveillance, especially among women who initiate PrEP outside research settings. We analyzed data from three recent PrEP safety and/or implementation studies that enrolled women who initiated PrEP within routine health clinics in Western Kenya to summarize perinatal outcomes following PrEP exposure in pregnancy.

Methods:

We utilized data from participants in PrIMA, PrIMA-X, and mWACh-PrEP studies who were ≥ 15 years, HIV negative, remained pregnant until at least 24 weeks gestation, and enrolled ≤32 weeks gestation. We summarized frequency of and compared each pregnancy outcome (stillbirth, preterm birth, low birthweight, neonatal death, congenital anomalies) by study cohort, PrEP exposure status (any vs. none), and timing of first PrEP exposure (first-, second-, or third-trimester exposure). In exploratory analyses, Poisson regression models were used to test whether timing of first PrEP exposure, timing of PrEP initiation (prior to pregnancy vs. during pregnancy), and duration of exposure in pregnancy were associated with adverse outcomes, adjusting for maternal age, primigravity, and clustered by study cohort as a random effect.

Results:

Data from 4,389 women were included in the analysis (29.8% with PrEP exposure). The median age was 24.1

years (IQR: 21.0, 28.6), and median gestational age at enrollment was 24 weeks (IQR: 20, 28). Most women (83.4%) were married and 39.4% had a partner of unknown HIV status. Among PrEP-exposed pregnancies (n=1310), most initiated PrEP in the second trimester (56.2%). Compared to pregnancies without PrEP exposure, preterm birth was less frequent among those with PrEP exposure in the first trimester (adjusted prevalence ratio [aPR]=0.49, 95% CI 0.42-0.57) and third-trimester (aPR=0.74, 95% CI 0.61-0.88) in exploratory analyses. Low birthweight was also lower among pregnancies with any PrEP exposure (aPR=0.77, 95% CI 0.61-0.97) and third-trimester exposure (aPR=0.74, 95% CI 0.61-0.88) compared to those with no exposure. Frequency of all other perinatal outcomes was comparable between pregnancies with and without PrEP exposure and did not differ by timing of exposure.

Conclusion:

We found no appreciable differences in perinatal outcomes by PrEP exposure, though PrEP- exposed pregnancies had lower frequency of some adverse outcomes. These findings support current guidelines recommending PrEP for pregnant and lactating women at risk of HIV.

Word Count: 2873/5500

Introduction

High HIV incidence among cisgender women of childbearing age remains a public health challenge in HIV high burden countries, including Kenya.(1–4) HIV acquisition risk doubles during pregnancy and postpartum compared to non-pregnant periods(5) due to biological alterations and social and behavioral factors.(2,3,5,6) The World Health Organization (WHO) and Kenya's Ministry of Health recommend offering daily oral tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis (PrEP) for HIV prevention to pregnant and lactating women at substantial ongoing risk for HIV acquisition, based on a large body of safety data on TDF use for HIV treatment among women living with HIV.(7–11) Existing safety data of prenatal HIV PrEP use among women without HIV are reassuring, finding no association between adverse perinatal outcomes and prenatal PrEP use.(12) Yet, safety studies to date focus on women who initiate PrEP during pregnancy, mostly in the second and third trimesters only(13–18), and do not evaluate gestational timing or duration of exposure. As oral TDF-based PrEP is scaling up among pregnant and breastfeeding women in East Africa with notable implementation successes in Kenya,(12,16), WHO emphasizes the need for further safety data, especially among women who initiate PrEP outside of research settings. Data from recent PrEP implementation studies among pregnant women could fill remaining safety evidence gaps, especially studies with participants who initiated PrEP in routine settings and prior to pregnancy.

Our team recently conducted three large PrEP safety and/or implementation studies among pregnant women in Western Kenya. The PrIMA Study (NCT03070600) enrolled 4447 pregnant participants at any time gestational age and offered PrEP (16.2%% initiated PrEP in pregnancy as part of study procedures).(19) The PrIMA Extension Study (PrIMA-X) included a novel cohort of 300 pregnant participants who initiated PrEP before or during pregnancy, yet prior to study enrollment. The mWACh-PrEP Study enrolled 600 participants who all initiated PrEP 24-32 weeks gestation within antenatal care. We conducted a descriptive prospective analysis using existing data from these studies with over 1300 PrEP-exposed pregnancies to summarize the frequency of adverse perinatal outcomes following PrEP exposure and to evaluate timing of PrEP exposure in pregnancy and perinatal outcomes among women in Kenya with and without PrEP exposure.

Methods

Study design and participants

This secondary analysis utilized data from participants enrolled in the PrIMA (PrEP Implementation for Mothers in Antenatal Care) study who did and did not initiate PrEP in pregnancy, novel ANC clients enrolled in the PrIMA-X (PrIMA Extension) study who initiated PrEP prior to or during pregnancy, and the mWACh-PrEP study (all participants initiated PrEP at 24-32 weeks gestation) to summarize frequency distributions of adverse perinatal outcomes across cohorts and PrEP exposure statuses. We utilized data collected from all studies up to April 2024 following the inclusion and exclusion criteria for the parent studies with additional criteria (**Table 1**).

Briefly, the PrIMA Study was a cluster randomized trial of PrEP counseling strategies conducted between January 2018 and July 2021 in 20 mother and child health clinics in Homa Bay and Siaya counties, Kenya (NCT03070600). The study protocol has been described in detail previously.(20) Briefly, antenatal care 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 9 months postpartum, regardless of PrEP use. For the current analysis, we used data from PrIMA participants who enrolled in the study at ≤32 weeks gestation and remained pregnant until at least 24 weeks gestation.

The PrIMA-X Study (R01 HD100201) is an ongoing longitudinal observational extension cohort study that evaluates safety of oral PrEP use during pregnancy and postpartum at four clinics in Western Kenya. PrIMA-X

study follows mother-child pairs up to 60 months post-birth. Women were recruited and enrolled into PrIMA-X study if they were at least 15 years old, HIV negative, and receiving maternal and child health (MCH) services at the participating study sites. The PrIMA-X study population consists of 1191 study participants, of whom 891 are mother-infant pairs previously enrolled in the PrIMA (R01AI125498) study. (21) An additional 300 pregnant women who initiated PrEP prior to pregnancy or during pregnancy and prior to enrollment were also enrolled at any gestational age who were not prior PrIMA participants, specifically to augment the number of participants with PrEP exposure during pregnancy. For the current analysis, we used data from these n=300 PrIMA-X participants who enrolled in the study at ≤32 weeks gestation, initiated PrEP prior to pregnancy or during the first trimester, and remained pregnant until at least 24 weeks gestation.

The mWACh-PrEP (R01 NR019220) study is an ongoing randomized trial conducted at 5 Maternal and Child Health (MCH) clinics in Siaya and Kisumu, Kenya, that seeks to improve PrEP adherence using mobile health strategies among women at risk for HIV who initiate PrEP during routine antenatal care. Pregnant women were eligible for enrollment if they were between 24-32 weeks gestation, aged ≥18 years, HIV negative, had an HIV risk score ≥6 (translating to HIV incidence 7.3 per 100 person-years),(22) initiated PrEP that day during ANC, planned to reside in the area for at least one year postpartum, and receive postnatal and infant care at the study clinic. Women who had previously used PrEP were not eligible for enrollment in the study.(23) mWACh-PrEP enrolled 600 women who initiated PrEP during pregnancy.

Data collection

At enrollment and during study visits, study nurses administer questionnaires using a tablet-based Research Electronic Data Capture (REDCap)(24) in English, Swahili or Dholuo languages as per the woman's preference. Questionnaires include assessment of sociodemographic characteristics, PrEP use information, and obstetric information. Participants self-reported male partner characteristics. Syphilis test results were abstracted from the participant's medical records. The duration of pregnancy was estimated between the first day of the last menstrual period to the date of delivery or pregnancy loss. Evaluation of peripartum outcomes was collected at the first study visit after birth (≤6 weeks) or end of pregnancy for each study participant. All perinatal outcomes (pregnancy loss, stillbirth, preterm birth, low birthweight, congenital anomalies, and neonatal death) were abstracted from clinical records or ascertained by study nurses who are trained in the collection of peripartum outcomes.

Study measures

Timing of first PrEP exposure in pregnancy was categorized as no PrEP exposure, first trimester (initiated PrEP prior to pregnancy or during the first trimester), second trimester, or third-trimester exposure. Among mWACh-PrEP participants, PrEP initiation date corresponded to the study enrollment date as all participants initiated PrEP same day during ANC as part of the parent study's inclusion criteria. All mWACh-PrEP participants who met the analysis' inclusion criteria were categorized as having second or third-trimester PrEP initiation. Among PrIMA and PrIMA-X participants, PrEP initiation date was ascertained at enrollment and/or follow-up, and timing of PrEP initiation in relation to pregnancy was calculated by subtracting the PrEP initiation date from the estimated pregnancy start date. Outcomes included preterm birth (<37 weeks) determined by last menstrual period, low birth weight (<2500g), stillbirth (pregnancy loss ≥24 weeks), congenital malformations, and neonatal death (death of a live-born infant within the first 28 days of life). We did not evaluate small-for-gestational-age due to >50% missingness of birth length. We evaluated each individual outcome in separate models.

Statistical analysis

Descriptive statistics were used to summarize frequency distributions of adverse pregnancy outcomes. We analyzed and compared each adverse pregnancy outcomes by study cohort, PrEP exposure status, and timing of PrEP exposure (no PrEP exposure, first, second, or third-trimester exposure) using Fisher's exact test for categorical variables (small for gestational age, stillbirth, neonatal death, congenital anomalies) and Wilcoxon rank-sum tests to compare the distribution of continuous variables (gestational age, weight at birth) to detect differences between exposure groups since we expect rare outcomes to occur in <5 cases in some groups.

In an exploratory analysis, we used separate Poisson regression models for each individual perinatal outcome to test whether timing of first PrEP exposure in pregnancy (no PrEP exposure vs. first, second, or third-trimester exposure) was associated with preterm birth, low birth weight, stillbirth, or small for gestational age. All models adjusted for study cohort *a priori*. We also conducted separate exploratory analyses to test whether timing of PrEP initiation (prior to pregnancy vs. during pregnancy) and duration of exposure (time from first PrEP exposure in pregnancy to discontinuation or birth/end of pregnancy) were associated with any adverse outcome. In each model, we accounted for maternal age at enrollment, primigravida, and clustered by study cohort as a random effect. Mode of delivery and infant sex were not included as adjustment variables due to the differential missingness of these variables across cohorts.

Ethical Considerations

Before commencement, the PrIMA, PrIMA-X, and mWACh-PrEP studies received approval from both the University of Washington Institutional Review Board (IRB) and the Kenyatta National Hospital and University of Nairobi Ethics and Research Committee (KNH-UoN ERC): PrIMA-X (P921/11/2019), mWACh-PrEP (P319/05/2021). All women who were interested in participating and met the eligibility criteria, provided written informed consent for their enrollment.

Results

In total, 4,389 women across the three cohorts met inclusion criteria and were included in the current analysis (82% of the overall combined study population). The median overall age was 24.1 years (IQR: 21.0,28.6), and the median gestational age at enrollment was 24 weeks (IQR: 20, 28). Most of the women (83.4%) were married with a median of 10 years of education (IQR: 8.0,12.0). There were differences in the frequency of being primigravida, having a partner known to be living with HIV, and self-reported PrEP adherence across studies (**Table 2**).

Among women with PrEP exposure during pregnancy (n=1310), most initiated PrEP in the second trimester (56.2%), followed by the third trimester (35.5%), first trimester (5.9%), and prior to pregnancy at 2.4%. The median duration of PrEP use during pregnancy was 12.4 weeks (IQR: 8.1,17.0), with participants from the PrIMA-X study reporting the highest median cumulative PrEP use at 20.2 weeks (IQR: 14.4, 27.7). Compared to PrIMA-X (97.9%) and mWACh PrEP (90.4%), the proportion of women in PrIMA still on PrEP at their last pregnancy visit was slightly lower at 84.5%.

Across all cohorts, rates ranged from 1.5%-2.7% for stillbirth, 15.1%-16.9% for preterm birth, 1.4%-3.1% for low birthweight, 10.5%-15.2% for small for gestational age, 0.4%-0.8% for any congenital anomalies, and 1.6%-1.7% for neonatal death. Furthermore, there were no significant differences in adverse perinatal outcomes between women without PrEP exposure and any cohort with PrEP exposure (**Table 3**). Similarly, there were no appreciable differences in the frequency of adverse outcomes by timing of PrEP exposure in pregnancy (**Table 4**).

In exploratory analyses, there was no statistically significant association between stillbirth occurrence and the timing of first PrEP exposure (p=0.976 for the second trimester and p=0.956 for the third trimester), cumulative PrEP use (p=0.883), or any PrEP exposure during pregnancy (p=0.617), compared to no PrEP exposure. Similarly, there was no statistically significant association between the frequency of preterm birth with cumulative PrEP use (p=0.082) or PrEP exposure in the second trimester (p=0.930). However, preterm birth was less frequent among those with PrEP exposure in the first trimester (adjusted prevalence ratio[aPR]=0.49, 95% CI 0.42-0.57, p<0.001) and third trimester (aPR=0.74, 95% CI 0.61-0.88, p=0.001), compared to those without any PrEP exposure in pregnancy. Compared to women without PrEP exposure in pregnancy, the frequency of low birthweight was lower among those with any PrEP exposure in pregnancy (aPR=0.77, 95% CI 0.61-0.97, p=0.027) and those with PrEP exposure in the third trimester (aPR=0.74, 95% CI 0.61-0.88, p=0.001). We did not detect associations between perinatal outcomes and any other PrEP exposure category (**Table 5**).

Discussion

Our study summarizes safety data for prenatal daily oral PrEP use in ongoing and recently completed studies which include characterization of the timing and duration of PrEP exposure during pregnancy among women in Kenya. Our evaluation contributes novel data from over 1300 PrEP-exposed pregnancies across three large studies and found no appreciable differences in the frequency of adverse perinatal outcomes between women with and without PrEP exposure. Specifically, rates of stillbirth, congenital malformations, and neonatal death were comparable across PrEP exposure statuses, with less frequent preterm birth and low birth weight among women with PrEP exposure during pregnancy. These findings are consistent with existing safety data, (3,12,15) and extends the evidence base by including data from women who initiated PrEP prior to pregnancy and during the first trimester. Our findings contribute to the growing body of evidence supporting that prenatal PrEP use appears safe among women initiating PrEP outside of research settings, further solidifying that daily oral PrEP is a safe and effective HIV prevention option for pregnant women.

Most safety studies to date categorize prenatal PrEP exposure as 'any' PrEP exposure during pregnancy versus none, without characterizing variance in timing of exposure. Early discontinuation among women who initiate PrEP during pregnancy and sub-optimal PrEP adherence are well-documented in existing PrEP in pregnancy studies, mainly from Kenya and South Africa(25), signaling that true prenatal exposure is likely highly variable. We did not detect differences in adverse perinatal outcomes by any PrEP exposure status or by timing or duration of PrEP exposure. A recent randomized trial in South Africa comparing immediate HIV oral PrEP initiation among pregnant women at 14-28 weeks gestation to women who deferred initiation of PrEP until breastfeeding cessation found no association between PrEP exposure and preterm birth or small for gestational age.(3) Similarly, two recent studies, one from Kenya and one from South Africa, also found that prenatal PrEP exposure confirmed with quantified tenofovir metabolites in dried blood spots was not associated with adverse pregnancy outcomes,(26,27) though the number of confirmed PrEP-exposed pregnancies was limited in both studies. Our findings add to the limited data on perinatal outcomes following well-characterized timing and duration of PrEP exposure. More studies with sample sizes large enough to compare pregnancy outcomes following different timing and duration of PrEP use in pregnancy, ideally with quantified PrEP exposure, would help complete the profile of prenatal PrEP use.

We did not detect differences in most perinatal outcomes among women with periconception or first-trimester PrEP exposure compared to those with no exposure or with exposure at later gestational ages. Few data exist on women who became pregnant while on PrEP and are mostly from early PrEP clinical trials in which participants discontinued PrEP upon becoming pregnant,(13) therefore limiting PrEP exposure to a very short period near periconception. One small study (n=35) of women on PrEP who continued use throughout pregnancy found no association between PrEP and adverse perinatal outcomes.(15) To our knowledge, no prior studies to date compare perinatal outcomes among women who initiate PrEP prior to and during pregnancy. The first trimester is a critical window when substantial fetal growth and development occur,(25,28) though limited data are available on pregnancy outcomes following first-trimester PrEP exposure. In contrast to safety evaluations of other antiretroviral drugs which suggested that first-trimester exposure might be linked to adverse outcomes compared to exposure later in pregnancy.(29,30) Our study found no association between PrEP exposure before pregnancy or during the first trimester and adverse perinatal outcomes. Our results provide reassuring evidence regarding the safety of PrEP use during pregnancy.

Our study has some limitations. The mWACh-PrEP study enrolled pregnant women from 24 weeks gestation and subsequently data from the study cannot evaluate the effect of early PrEP exposure on pregnancy losses prior to 24 weeks. To prevent immortal time bias among PrIMA and PrIMA-X participants and to create a comparable cohort, we only included PrIMA and PrIMA-X participants who had a study visit while still pregnant that occurred 24-32 weeks. Therefore, our sample may have a survivorship bias and we could not evaluate early pregnancy loss across cohorts. Additionally, some variables related to perinatal outcomes (e.g., infant sex, birth length, mode of delivery) were incomplete with differential missingness across studies, which limited the outcomes and adjustment variables available for analysis in the dataset. However, data were mostly complete (<10% missingness) for the primary outcomes included. Lastly, the reliance on self-reported data for PrEP

adherence may introduce reporting biases. Despite these limitations, our study contributes descriptive data from a large population of PrEP-exposed pregnancies and the use of data from routine clinical settings enhances the generalizability of our findings to real-world populations. At the time of our evaluation, only daily oral PrEP was available outside of research settings in Kenya and therefore we are unable to describe exposure to other PrEP methods. The prospective design and the inclusion of multiple cohorts also strengthen the validity of our results, adding to a growing pool of safety evidence.

Conclusion

In conclusion, our study found that the frequency of adverse perinatal outcomes was similar among women with and without PrEP exposure during pregnancy, regardless of the timing of PrEP exposure, with lower rates of preterm birth and low birth weight among PrEP-exposed pregnancies. These findings provide reassurance regarding the safety of PrEP use throughout pregnancy and support current guidelines recommending PrEP for pregnant and lactating women at risk of HIV.

References:

1. Graybill LA, Kasaro M, Freeborn K, Walker JS, Poole C, Powers KA, et al. Incident HIV among pregnant and breast-feeding women in sub-Saharan Africa: a systematic review and meta-analysis. AIDS. 2020 Apr 1;34(5):761–76.

2. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. 2014 Feb;11(2):e1001608.

3. Moodley D, Lombard C, Govender V, Naidoo M, Desmond AC, Naidoo K, et al. Pregnancy and neonatal safety outcomes of timing of initiation of daily oral tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis for HIV prevention (CAP016): an open-label, randomised, non-inferiority trial. Lancet HIV. 2023 Mar;10(3):e154–63.

4. Birdthistle I, Tanton C, Tomita A, de Graaf K, Schaffnit SB, Tanser F, et al. Recent levels and trends in HIV incidence rates among adolescent girls and young women in ten high-prevalence African countries: a systematic review and meta-analysis. Lancet Glob Health. 2019 Nov;7(11):e1521–40.

5. Thomson KA, Hughes J, Baeten JM, John-Stewart G, Celum C, Cohen CR, et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. J Infect Dis. 2018 Jun 5;218(1):16–25.

6. Marston M, Risher K, Mahy MI. HIV acquisition in pregnancy: implications for mother-to-child transmission at the population level in sub-Saharan Africa. J Int AIDS Soc. 2021 Sep;24 Suppl 5(Suppl 5):e25783.

7. Bekker LG, Brown B, Joseph-Davey D, Gill K, Moorhouse M, Delany-Moretlwe S, et al. Southern African guidelines on the safe, easy and effective use of pre-exposure prophylaxis: 2020. South Afr J HIV Med. 2020 Dec 10;21(1):1152.

8. Kinuthia J, Pintye J, Abuna F, Mugwanya KK, Lagat H, Onyango D, et al. Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme. Lancet HIV. 2020 Jan;7(1):e38–48.

9. Zimba C, Maman S, Rosenberg NE, Mutale W, Mweemba O, Dunda W, et al. The landscape for HIV pre-exposure prophylaxis during pregnancy and breastfeeding in Malawi and Zambia: A qualitative study. PLoS One. 2019;14(10):e0223487.

10. WHO-HIV-2017.09-eng.pdf [Internet]. [cited 2024 Feb 22]. Available from: https://iris.who.int/bitstream/handle/10665/255866/WHO-HIV-2017.09-eng.pdf

11. ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018.pdf [Internet]. [cited 2024 Feb 22]. Available from: https://cquin.icap.columbia.edu/wp-content/uploads/2017/04/ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018.pdf

12. Joseph Davey DL, Pintye J, Baeten JM, Aldrovandi G, Baggaley R, Bekker LG, et al. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? J Int AIDS Soc. 2020 Jan;23(1):e25426.

13. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA. 2014 Jul 23;312(4):362–71.

14. Callahan R, Nanda K, Kapiga S, Malahleha M, Mandala J, Ogada T, et al. Pregnancy and contraceptive use among women participating in the FEM-PrEP trial. J Acquir Immune Defic Syndr. 2015 Feb 1;68(2):196–203.

15. Heffron R, Mugo N, Hong T, Celum C, Marzinke MA, Ngure K, et al. Pregnancy outcomes and infant growth among babies with in-utero exposure to tenofovir-based preexposure prophylaxis for HIV prevention. AIDS. 2018 Jul;32(12):1707–13.

16. Pintye J, Kinuthia J, Roberts DA, Wagner AD, Mugwanya K, Abuna F, et al. Brief Report: Integration of PrEP Services Into Routine Antenatal and Postnatal Care: Experiences From an Implementation Program in Western Kenya. J Acquir Immune Defic Syndr. 2018 Dec 15;79(5):590–5.

17. Dettinger JC, Kinuthia J, Pintye J, Abuna F, Begnel E, Mugwanya K, et al. Perinatal outcomes following maternal pre-exposure prophylaxis (PrEP) use during pregnancy: results from a large PrEP implementation program in Kenya. J Int AIDS Soc. 2019 Sep;22(9):e25378.

18. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. AIDS. 2017 Jan 14;31(2):213–32.

19. Kinuthia J, Dettinger JC, Stern J, Ngumbau N, Ochieng B, Gómez L, et al. Risk-based versus universal PrEP delivery during pregnancy: a cluster randomized trial in Western Kenya from 2018 to 2019. J Int AIDS Soc. 2023 Feb;26(2):e26061.

20. Dettinger JC, Kinuthia J, Pintye J, Mwongeli N, Gómez L, Richardson BA, et al. PrEP Implementation for Mothers in Antenatal Care (PrIMA): study protocol of a cluster randomised trial. Vol. 9, BMJ Open. 2019. p. e025122.

21. Dettinger JC, Kinuthia J, Pintye J, Mwongeli N, Gómez L, Richardson BA, et al. PrEP Implementation for Mothers in Antenatal Care (PrIMA): study protocol of a cluster randomised trial. BMJ Open. 2019 Mar 7;9(3):e025122.

22. Pintye J, Drake AL, Kinuthia J, Unger JA, Matemo D, Heffron RA, et al. A Risk Assessment Tool for Identifying Pregnant and Postpartum Women Who May Benefit From Preexposure Prophylaxis. Clin Infect Dis. 2017 Mar 15;64(6):751–8.

23. Mogaka JN, Otieno FA, Akim E, Beima-Sofie K, Dettinger J, Gomez L, et al. A Text Messaging-Based Support Intervention to Enhance Pre-exposure Prophylaxis for HIV Prevention Adherence During Pregnancy and Breastfeeding: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2023 Jan 30;12:e41170.

24. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019 Jul;95:103208.

25. Jao J, Abrams EJ. Metabolic Complications of in utero Maternal HIV and Antiretroviral Exposure in HIV-Exposed Infants. Pediatr Infect Dis J. 2014 Jul;33(7):734–40.

26. Gomez LA. Evaluating the association of prenatal PrEP exposure with perinatal and growth outcomes from infancy through early childhood [Internet] [Thesis]. 2023 [cited 2024 Feb 25]. Available from: https://digital.lib.washington.edu:443/researchworks/handle/1773/50417

27. Joseph Davey DL, Nyemba DC, Mvududu R, Mashele N, Johnson L, Bekker LG, et al. Pregnancy outcomes following self-reported and objective-measured exposure to oral preexposure prophylaxis in South Africa. AIDS. 2024 Jan 1;38(1):75–83.

28. Steegers-Theunissen RPM, Twigt J, Pestinger V, Sinclair KD. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. Hum Reprod Update. 2013;19(6):640–55.

29. Lockman S, Brummel SS, Ziemba L, Stranix-Chibanda L, McCarthy K, Coletti A, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet. 2021 Apr 3;397(10281):1276–92.

30. Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, et al. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827–40.

APPENDIX: TABLES AND FIGURES

Table 1. Inclusion and exclusion criteria by study cohort

	PrIMA participants (n=3595)	PrIMA-X participants (n=242)	mWACh-PrEP participants (n=600)
Parent study	Inclusion • Currently pregnant (any gestational age) • Not using PrEP at enrollment • ≥15 years old • HIV negative • Receiving MCH services at study sites	Inclusion • Currently pregnant (any gestational age) • Currently using PrEP • ≥15 years old • HIV negative • Receiving MCH services at study sites	Inclusion • Currently pregnant (24-32 weeks gestation) • Initiating PrEP today during ANC • ≥18 years old • HIV negative • Receiving MCH services at study sites • High HIV risk score (≥6)
Current analysis	Inclusion • Pregnancy outcome data available • PrEP use data available. • Remained pregnant until at least 24 weeks Exclusion • Multiple pregnancy • Seroconverted during pregnancy. • Terminated study during pregnancy. • Missing PrEP use data • Initiated PrEP postpartum • Pregnancy loss <24 weeks gestation • Enrolled >32 weeks gestation	Inclusion • Pregnancy outcome data available • PrEP use data available. • Initiated PrEP prior to pregnancy or during pregnancy • Remained pregnant until at least 24 weeks Exclusion • Multiple pregnancy • Seroconverted during pregnancy. • Terminated study during pregnancy. • Missing PrEP use data • Initiated PrEP in 2nd/3rd trimester. • Pregnancy loss <24 weeks gestation • Enrolled >32 weeks gestation	Inclusion • Pregnancy outcome data available • PrEP use data available. Exclusion • Multiple pregnancy • Seroconverted during pregnancy. • Terminated study during pregnancy. • Missing PrEP use data

Figure 1a. Flow diagram of enrollment into studies and participant inclusion in current analyses (PrIMA-X and mWACh-PrEP)

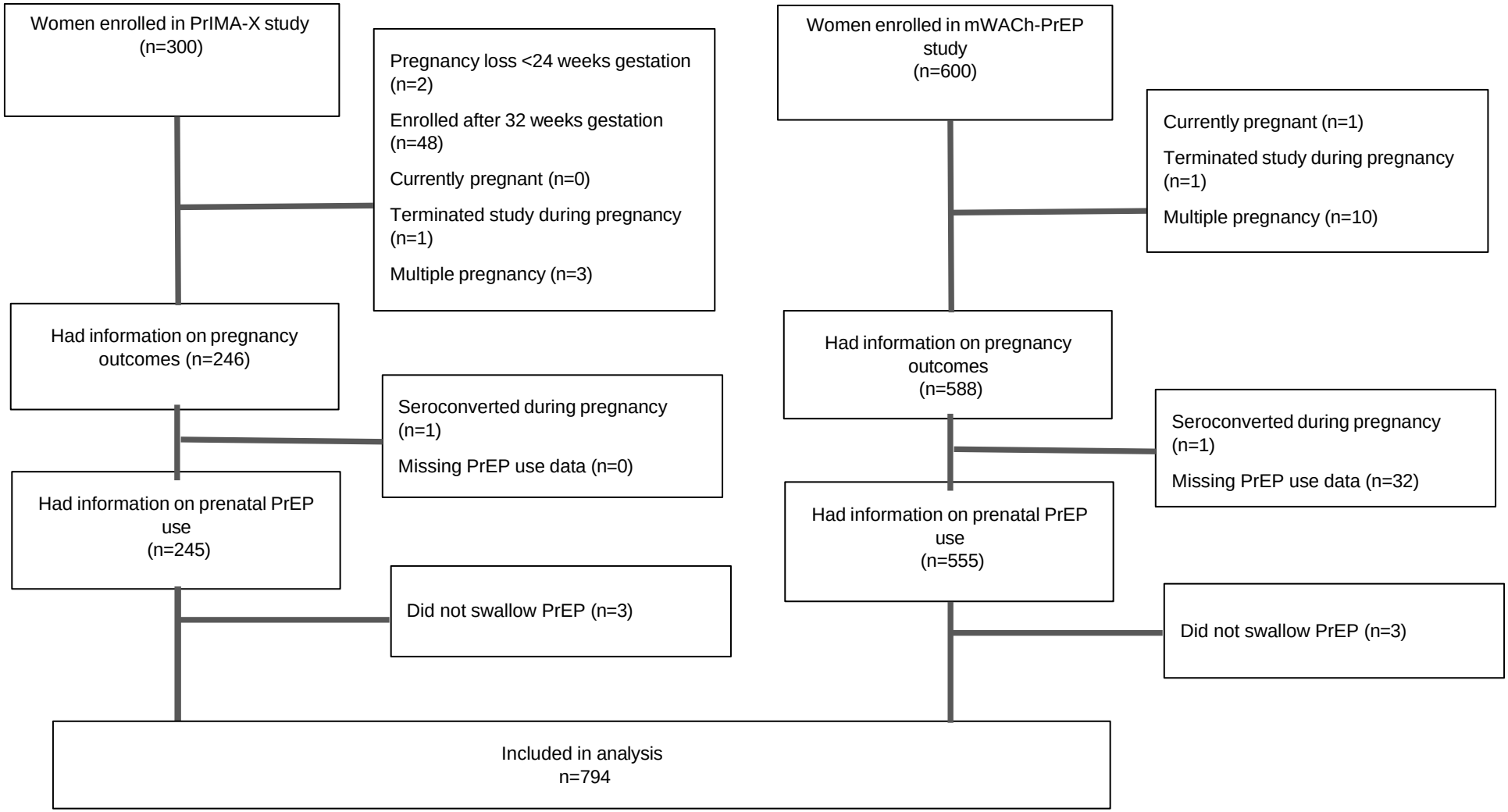

Figure 1b. Flow diagram of enrollment into studies and participant inclusion in current analyses (PrIMA)

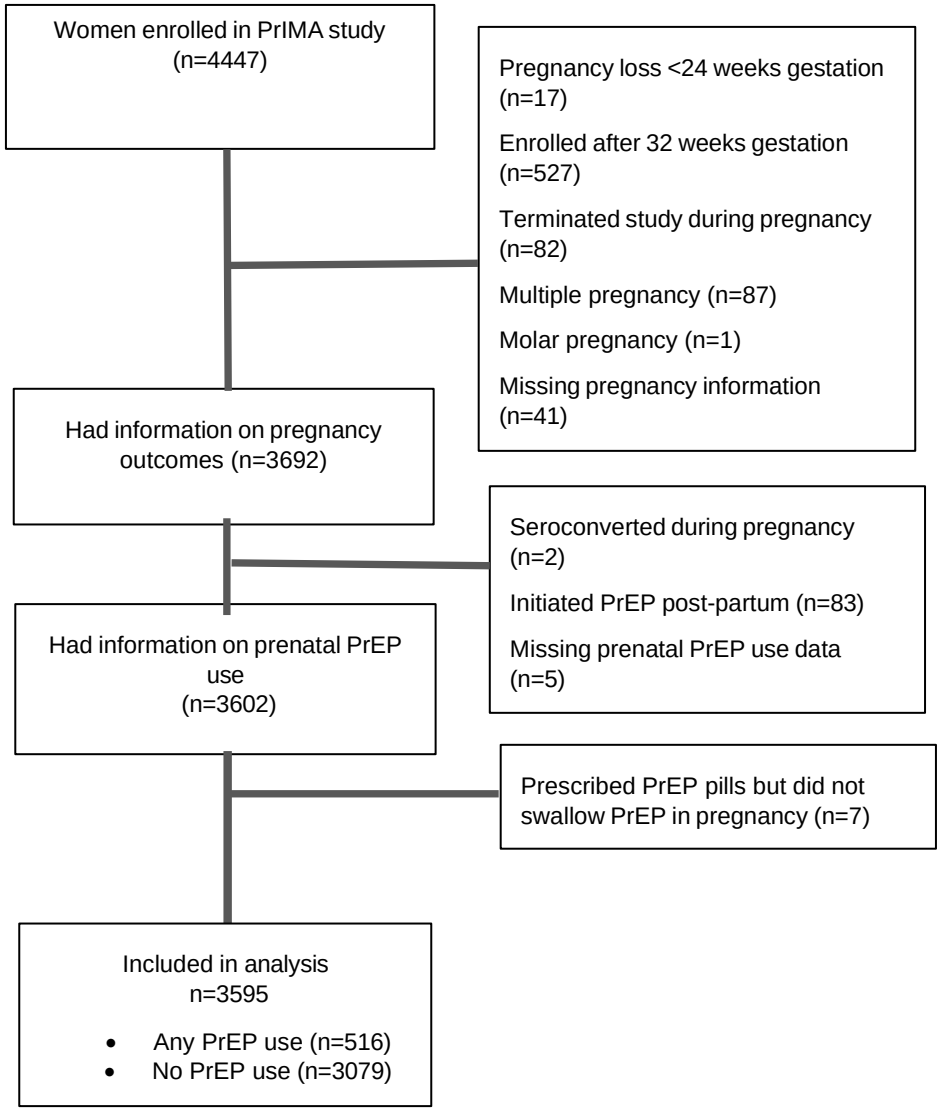

Table 2. Characteristics of participants included in the analysis (n=4389)

Demographics	n (%) or Median (IQR)				
	Overall (n=4389)	No PrEP exposure (n=3079)	Any PrEP exposure		
			PrIMA (n=516)	PrIMA-X (n=242)	mWACh-PrEP (n=552)
Women age(years)	24.1 (21, 28.6)	23.9 (20.9, 28)	25 (21, 30.2)	25.9 (23.0, 29.9)	24.8 (21.5, 29.2)
<24 years	2125 (48.4)	1563 (50.8)	218 (42.3)	91 (37.6)	253 (45.8)
24-35	2028 (46.2)	1383 (44.9)	257 (49.8)	125 (51.7)	263 (47.6)
≥35 years	230 (5.2)	131 (4.3)	41 (8.0)	22 (9.1)	36 (6.5)
Missing	6 (0.1)	2 (0.1)	0 (0)	4 (1.7)	0 (0)
Currently married					
No	685 (15.6)	60 (14.5)	60 (11.6)	17 (7.0)	161 (29.2)
Yes	3662 (83.4)	2595 (84.3)	452 (87.6)	225 (93.0)	390 (70.7)
Missing	42 (1.0)	37 (1.2)	4 (0.8)	0 (0)	1 (0.2)
Marriage type					
Monogamous	3178 (86.8)	2298 (88.6)	339 (75.0)	192 (85.3)	349 (89.5)
Polygamous	464 (12.7)	282 (10.9)	110 (24.3)	32 (14.2)	40 (10.3)
Prefer not to answer	3 (0.1)	2 (0.1)	0 (0)	0 (0)	1 (0.3)
Missing	17 (0.5)	13 (0.5)	3 (0.7)	1 (0.4)	0 (0)
Completed education (years)	10 (8, 12)	10 (8, 12)	9 (8, 12)	9 (8, 12)	12 (9, 13)
Partner HIV status					
HIV-positive	211 (4.8)	45 (1.5)	104 (20.2)	47 (19.4)	15 (12.7)
HIV negative	2402 (54.7)	2080 (67.6)	200 (38.8)	110 (45.5)	12 (2.2)
Unknown	1728 (39.4)	913 (29.7)	209 (40.5)	81 (33.5)	525 (95.1)
No partner/missing	48 (1.1)	41 (1.3)	3 (0.6)	4 (1.7)	0 (0)
Pregnancy history					
Gestational age at enrollment (weeks)	24 (20, 28)	24 (19, 28)	24 (18, 28)	24 (18, 28)	26 (24, 29)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Determination of gestational age					
LMP	3843 (87.6)	3016 (98.0)	504 (97.7)	88 (36.4)	235 (42.3)
Fundal height	503 (11.5)	63 (2.1)	12 (2.3)	146 (60.3)	282 (51.1)
Ultrasound	0 (0)	0 (0)	0 (0)	8 (3.3)	35 (6.3)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No. of ANC visits attended to date at enrollment	2 (1, 3)	2 (1, 2)	1 (1, 2)	2 (2, 3)	2 (2, 3)
Primigravida					
No	3250 (74.1)	2244 (72.9)	438 (84.9)	217 (89.7)	351 (63.6)
Yes	1123 (25.6)	820 (26.6)	77 (14.9)	25 (10.3)	201 (36.4)
Missing	16 (0.4)	15 (0.5)	1 (0.2)	0 (0)	0 (0)

No. of pregnancies	2 (1, 4)	2 (1,3)	3 (2, 4)	3 (2, 4)	2 (1, 3)
Mode of delivery					
Vaginal	3348 (76.3)	2303 (74.8)	399 (77.3)	217 (89.7)	429 (77.7)
C-section	255 (5.8)	138 (4.5)	25 (4.8)	20 (8.3)	72 (13.0)
Missing/Unknown	786 (17.9)	638 (20.7)	92 (17.8)	5 (2.1)	51 (9.2)
Infant sex					
Male	1942 (44.3)	1311 (42.6)	231 (44.8)	125 (51.7)	275 (49.8)
Female	1981 (45.1)	1374 (44.6)	225 (43.6)	113 (46.7)	269 (48.7)
Missing/Unknown	466 (10.6)	394 (12.8)	60 (11.6)	4 (1.7)	8 (1.5)
Birth history among those with prior pregnancies [2]					
No. of live births	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Total number of living children	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 2)
Prior miscarriages / stillbirth					
No	2687 (82.7)	1874 (83.5)	357 (81.5)	173 (79.7)	283 (80.6)
Yes	550 (16.9)	367 (16.4)	80 (18.3)	35 (16.1)	68 (19.4)
Missing	13 (0.4)	3 (0.1)	1 (0.2)	9 (4.2)	0 (0.0)
PrEP use					
Cumulative PrEP use in pregnancy (weeks) [3]	12.4 (8.1, 17)	-	10.3 (6, 15.6)	20.2 (14.4, 27.7)	11.7 (8.3, 15.1)
Timing of PrEP initiation					
Never initiated PrEP	3079 (70.2)	3079 (100)	0 (0)	0 (0)	0 (0)
Prior to pregnancy	32 (2.4)	0 (0)	0 (0)	32 (13.2)	0 (0)
1st trimester	77 (5.9)	0 (0)	25 (4.8)	43 (17.8)	0 (0)
2nd trimester	736 (56.2)	0 (0)	252 (48.8)	144 (59.5)	317 (57.4)
3rd trimester	465 (35.5)	0 (0)	239 (46.3)	23 (9.5)	235 (42.6)
PrEP status at last ANC visit [4]					
Never on PrEP	3079 (70.2)	3079 (100)	0 (0)	0 (0)	0 (0)
On PrEP	1172 (26.7)	0 (0)	436 (84.5)	237 (97.9)	499 (90.4)
Unknown/missing	58 (1.3)	0 (0)	5 (1.0)	1 (0.4)	52 (9.4)
Discontinued	80 (1.8)	0 (0)	75 (14.5)	4 (1.7)	1 (0.2)
Self-reported PrEP adherence in last 30 days at last ANC visit [5]					
Never on PrEP	3079 (71.1)	3079 (100)	0 (0)	0 (0)	0 (0)
No missed pills	747 (17.3)	0 (0)	296 (57.4)	187 (77.6)	264 (52.8)
Any missed pills	421 (9.7)	0 (0)	140 (27.1)	48 (19.9)	233 (46.6)
No PrEP use	81 (1.9)	0 (0)	75 (14.5)	5 (2.1)	1 (0.2)
Missing	3 (0.1)	0 (0)	5 (1.0)	1 (0.4)	2 (0.4)
PrEP formulation(s) dispensed during pregnancy					
Never on PrEP	3079 (70.2)	3079 (100)	0 (0)	0 (0)	0 (0)

TDF/FTC (300mg/200mg) only	917 (20.9)	0 (0)	182 (35.3)	233 (96.3)	502 (90.9)
TDF 300mg only	3 (0.1)	0 (0)	3 (0.6)	0 (0)	0 (0)
TDF/3TC (300mg/300mg) only	83 (1.9)	0 (0)	24 (4.7)	9 (3.7)	50 (9.1)
Combination	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	307 (7.0)	0 (0)	307 (59.5)	0 (0)	0 (0)

PrEP=pre-exposure prophylaxis for HIV prevention; ANC=antenatal care

[1] Polygamous marriage was evaluated among those who are married
[2] Pregnancy and obstetric history assessed among those with history of prior pregnancy at enrollment
[3] From date of PrEP initiation until date of PrEP discontinuation for mothers who discontinued PrEP use, or pregnancy end date for mothers who continued PrEP
[4] At last study visit attended during pregnancy after PrEP initiation
[5] Among women with PrEP status known at last study visit attended during pregnancy. No PrEP use includes women who previously discontinued PrEP.

Table 3. Birth and neonatal outcomes by PrEP exposure in pregnancy and cohort (n=3595 from PrIMA; n=552 from mWACh-PrEP; n=242 from PrIMA-X)

		n (%) or median IQR			
			Any PrEP exposure		
	N	No PrEP Exposure [2] (n=3079)	PrIMA (n=516)	PrIMA-X (n=242)	mWACh-PrEP (n=552)
Pregnancy and birth outcomes					
Any pregnancy loss	4389	64 (2.1)	14 (2.7)	4 (1.7)	8 (1.5)
Stillbirth (>24 weeks)	4389	64 (2.1)	14 (2.7)	4 (1.7)	8 (1.5)
Gestational age at birth	4352	38 (37, 39)	38 (37.9, 39)	38 (38, 39)	39.4 (37.9, 41)
Preterm (<37 weeks)	4352	593 (19.3)	87 (16.9)	36 (15.1)	84 (16.2)
Birth weight (kg)*	2872	3.4 (3, 3.6)	3.3 (3, 3.6)	3.2 (2.9, 3.5)	3.2 (2.9, 3.5)
Birth weight <2.5 kg*	2872	47 (2.5)	5 (1.4)	4 (3.1)	10 (2.1)
Birth length (cm)*	1403	50 (50, 52)	50 (50, 52)	50 (49, 50.09)	49.5 (48, 50)
Any congenital anomalies*	4299	23 (0.8)	4 (0.8)	1 (0.4)	2 (0.4)
Cleft lip/pallate*	4299	13 (0.4)	3 (0.6)	0 (0.0)	0 (0)
Other mouth/gum*	4299	2 (0.1)	0 (0)	0 (0)	0 (0)
Club foot*	4299	3 (1.0)	0 (0)	0 (0)	2 (0.4)
Jointed fingers or toes*	4299	2 (0.1)	1 (0.2)	0 (0)	0 (0)
Extra fingers or toes*	4299	4 (0.1)	0 (0)	0 (0)	0 (0)
Missing finger*	4299	0 (0)	0 (0)	1 (0.4)	0 (0)
Other limb*	4299	3 (0.1)	0 (0)	0 (0)	0 (0)
Infant postnatal outcomes					
6-week growth indicators[3]*					
Length z-score <-2*	2827	182 (9.6)	27 (10.0)	22 (10.1)	40 (9.0)
Weight z-score <-2*	2873	56 (2.9)	6 (2.2)	10 (4.6)	17 (3.8)
Neonatal death*	4299	43 (1.4)	8 (1.6)	4 (1.7)	9 (1.7)

* Among 4299 live births

[1] Includes PrIMA clients who never took PrEP during pregnancy

[2] Includes new ANC clients from PrIMA-X and mWACh-PrEP client who initiated PrEP the 2nd trimester

[3] Includes new ANC clients from PrIMA-X and mWACh-PrEP client who initiated PrEP the 3rd trimester

[4] Includes pregnancy loss, PTB, LBW, SGA, and congenital anomalies

Table 4. Birth and neonatal outcomes by timing of first PrEP exposure in pregnancy (n=3595 from PrIMA; n=552 from mWACh-PrEP; n=242 from PrIMA-X)

		n (%) or median IQR			
			Any PrEP exposure		
	N	No PrEP Exposure [1] (n=3079)	1st trimester [2] (n=109)	2nd trimester [3] (n=736)	3rd trimester [4] (n=465)
Pregnancy and birth outcomes					
Any pregnancy loss	4389	64 (2.1)	0 (0)	16 (2.2)	10 (2.2)
Stillbirth (>24 weeks)	4389	64 (2.1)	0 (0)	16 (2.2)	10 (2.2)
Gestational age at birth	4352	38 (37, 39)	38 (38, 39)	38.1 (37.6, 40)	38.3 (38, 40)
Preterm (<37 weeks)	4352	593 (19.3)	10 (9.2)	134 (18.9)	63 (13.9)
Birth weight (kg)*	2872	3.4 (3, 3.6)	3.3 (3, 3.5)	3.3 (3, 3.5)	3.2 (3, 3.5)
Birth weight <2.5 kg*	2872	47 (2.5)	2 (3.1)	9 (1.7)	8 (2.2)
Birth length (cm)*	1403	50 (50, 52)	50 (49, 50.8)	50 (48.6, 50)	50 (49, 50.2)
Any congenital anomalies*	4299	23 (0.8)	1 (0.9)	4 (0.6)	2 (0.4)
Cleft lip/pallate*	4299	13 (0.4)	0 (0)	2 (0.3)	1 (0.2)
Other mouth/gum*	4299	2 (0.1)	0 (0)	0 (0)	0 (0)
Club foot*	4299	3 (1.0)	0 (0)	1 (0.1)	1 (0.2)
Jointed fingers or toes*	4299	2 (0.1)	1 (0.9)	0 (0)	0 (0)
Extra fingers or toes*	4299	4 (0.1)	0 (0)	0 (0)	0 (0)
Missing finger*	4299	0 (0)	0 (0)	1 (0.4)	0 (0)
Other limb*	4299	3 (0.1)	0 (0)	0 (0)	0 (0)
Infant postnatal outcomes					
6-week growth indicators[3]*					
Length z-score <-2*	2827	182 (9.6)	5 (5.2)	56 (10.5)	28 (9.3)
Weight z-score <-2*	2873	56 (2.9)	2 (2.1)	20 (3.7)	11 (3.6)
Neonatal death*	4299	43 (1.4)	0 (0)	18 (1.8)	8 (1.8)

* Among 4299 live births

[1] Includes PrIMA clients who never took PrEP during pregnancy

[2] Includes PrIMA clients and new ANC clients from PrIMA-X who initiated PrEP prior to pregnancy or during the 1st trimester

[3] Includes PrIMA clients, new ANC clients from PrIMA-X, and mWACh-PrEP clients who initiated PrEP the 2nd trimester

[4] Includes PrIMA clients, new ANC clients from PrIMA-X, and mWACh-PrEP clients who initiated PrEP the 3rd trimester

Table 5: Association between timing of first PrEP exposure in pregnancy and adverse perinatal outcomes

Adverse perinatal outcomes	Adverse pregnancy outcome		Univariable Poisson regression		Multivariable Poisson regression [1]	
	Yes	No	Prevalence Ratio (95% CI)	p-value	Adj. Prevalence Ratio [1] (95% CI)	p-value
Stillbirth (n=4389)	90 (2.1%)	4299 (98.0%)				
PrEP exposure in pregnancy						
No PrEP exposure	64 (2.1%)	3015 (97.9%)	ref		ref	
Any PrEP exposure	26 (2.0%)	1284 (98.0%)	0.95 (0.66-1.38)	0.804	0.91 (0.63-1.31)	0.617
Cumulative PrEP use in pregnancy – all participants (weeks, n=4389) [3]	0 (0, 7)	0 (0, 6.3)	0.99 (0.97-1.01)	0.189	0.99 (0.97-1.00)	0.060
Cumulative PrEP use in pregnancy – only those who used PrEP in pregnancy (weeks, n=1310) [3]	11.9 (8.1, 15.1)	12.4 (8.1, 17)	0.97 (0.93-1.02)	0.223	0.97 (0.68-1.39)	0.883
Timing of first PrEP exposure						
No PrEP exposure	64 (2.1%)	3015 (97.9%)	ref		ref	
1st trimester	0 (0.0%)	109 (100.0%)	-	-	-	-
2nd trimester	16 (2.2%)	720 (97.8%)	1.05 (0.79-1.39)	0.756	1.00 (0.74-1.33)	0.976
3rd trimester	10 (2.2%)	455 (97.9%)	1.03 (0.56-1.90)	0.913	0.98 (0.52-1.85)	0.956
Preterm birth (n=4352)	800 (18.4%)	3552 (81.6%)				
PrEP exposure in pregnancy						
No PrEP exposure	593 (19.3%)	2486 (80.7%)	ref		ref	
Any PrEP exposure	207 (16.3%)	1066 (83.7%)	0.84 (0.81-0.88)	<0.001	Convergence not achieved	
Cumulative PrEP use in pregnancy all participants (weeks, n=4352) [3]	0 (0, 3.5)	0 (0, 6.8)	0.98 (0.96-0.99)	0.003	0.98 (0.97-0.99)	0.003
Cumulative PrEP use in pregnancy – only those who used PrEP in pregnancy (weeks, n=1273) [3]	9.6 (6.6, 13.9)	12.9 (8.4, 17)	0.96 (0.92-1.00)	0.064	0.96 (0.92-1.01)	0.082
Timing of first PrEP exposure						
No PrEP exposure	593 (19.3%)	2486 (80.7%)	ref		ref	
1st trimester	10 (9.2%)	99 (90.8%)	0.48 (0.39-0.58)	<0.001	0.49 (0.42-0.57)	<0.001
2nd trimester	134 (18.9%)	575 (81.1%)	0.98 (0.87-1.11)	0.766	0.99 (0.89-1.11)	0.930
3rd trimester	63 (13.9)	392 (86.2%)	0.72 (0.62-0.84)	<0.001	0.74 (0.61-0.88)	0.001
Low birthweight (n=2872) [2]	66 (2.3%)	2806 (97.7%)				
PrEP exposure in pregnancy						
No PrEP exposure	47 (2.5%)	1847 (97.5%)	ref		ref	
Any PrEP exposure	19 (1.9%)	959 (98.1%)	0.78 (0.60-1.02)	0.071	0.77 (0.61-0.97)	0.027

Adverse perinatal outcomes	Adverse pregnancy outcome		Univariable Poisson regression		Multivariable Poisson regression [1]	
	Yes	No	Prevalence Ratio (95% CI)	p-value	Adj. Prevalence Ratio [1] (95% CI)	p-value
Cumulative PrEP use in pregnancy, all participants (weeks, n=2872) [3]	0 (0, 4.4)	0 (0, 8.3)	0.98 (0.95-1.02)	0.406	0.98 (0.95-1.02)	0.360
Cumulative PrEP use in pregnancy – only those who used PrEP in pregnancy (weeks, n=978) [3]	12.7 (6, 14.4)	12 (8, 16.3)	0.99 (0.94-1.05)	0.817	0.99 (0.93-1.05)	0.800
Timing of first PrEP exposure						
No PrEP exposure	47 (2.5%)	1847 (97.5%)	ref		ref	
1st trimester	2 (3.1%)	62 (96.9%)	1.26 (0.58-2.75)	0.563	1.26 (0.56-2.84)	0.584
2nd trimester	9 (1.7%)	533 (98.3%)	0.67 (0.35-1.28)	0.222	0.65 (0.35-1.21)	0.179
3rd trimester	8 (2.2%)	364 (97.9%)	0.87 (0.75-1.00)	0.044	0.85 (0.76-0.94)	0.001

[1] Multivariable Poisson regression adjusted for maternal age at enrollment and primigravida at enrollment; all models accounted for clustering by including study cohort as a random-effect

[2] Among n=4299 live births; 66.8% live births were missing birthweight data