Delivery of Antiretroviral Pre-exposure Prophylaxis for HIV prevention in Pregnant and Postpartum Women

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Abstract

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Women in sub-Saharan Africa have substantial risk of acquiring HIV acquisition during and soon after pregnancy. Additionally, acute HIV infection among pregnant and breastfeeding women poses a double burden in that acute maternal HIV accounts for nearly one-third of all mother-to-child transmissions of HIV (MTCT). To reach global targets for elimination of MTCT and HIV prevention for mothers, it is critical to integrate effective primary HIV prevention strategies into maternal and child health (MCH) services. Tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis (PrEP) prevents HIV infection in adherent women. The World Health Organization (WHO) recommends PrEP for all individuals, including pregnant and breastfeeding women, at substantial HIV risk (defined as HIV residence in regions where HIV incidence is >3%). Programmatic delivery of PrEP for pregnant women is currently being considered in high-prevalence regions, though

implementation approaches that efficiently optimize the benefit of PrEP during pregnancy have not been defined. Additionally, although WHO guidelines support PrEP use in pregnancy, national committees have differed in their conclusions. For example, PrEP use during pregnancy is supported by Kenyan antiretroviral guidelines but the lack of complete safety data led PrEP to be contraindicated for pregnant women in the current South African PrEP guidelines. As countries expand programmatic delivery of PrEP to pregnant women, it is important to understand motivations and beliefs for using PrEP during pregnancy to address concerns unique to this population. The studies within this dissertation address the implementation science gaps described above for the delivery of PrEP for HIV prevention to pregnant and postpartum in sub-Saharan Africa.

To inform efficient PrEP delivery models, we present an empiric risk score for identifying pregnant and postpartum Kenyan women at highest risk for HIV acquisition who would mostly benefit from PrEP while reducing unnecessary exposure among low-risk women. Using data that could be easily collected in standard MCH clinic settings without additional laboratory diagnostics, our risk score identified 56% of pregnant women who acquired HIV among just 16% of women.

Using register data from 62 antenatal MCH facilities throughout Kenya, we further estimated the absolute number and proportion of HIV-uninfected pregnant women in Kenya who could be offered PrEP under different public health approaches, including offering PrEP universally or based on either regional HIV prevalence and/or individual-level HIV risk factors. We found that offering PrEP only to pregnant women in the region with highest HIV prevalence (Nyanza) would reduce PrEP use among low-risk women by 74%, but exclude 63% of women with high risk for HIV based on individual-level characteristics nationally.

To complement service delivery data, we also assessed experiences of using PrEP during pregnancy among HIV-uninfected Kenyan women in HIV-serodiscordant couples who became pregnant while using PrEP. The personal experiences of women with direct exposure to PrEP during

pregnancy offers valuable insights for informing development of effective PrEP messaging strategies and programs.

Finally, we evaluate whether adverse perinatal outcomes were more frequent in a cohort of Kenyan and Ugandan HIV-infected women who used TDF-containing antiretroviral therapy (ART) during pregnancy compared to HIV-infected women who used ART during pregnancy that did not contain TDF. Our findings support the growing evidence that prolonged prenatal TDF use is not associated with adverse perinatal outcomes and contribute to the few prospective studies evaluating the safety of TDF use during pregnancy from African cohorts.

The studies within this dissertation aim to address these implementation science gaps and inform optimal and effective delivery of PrEP for HIV prevention to pregnant and postpartum in sub-Saharan Africa.

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DEDICATION

To my parents and my mentors

CHAPTER 1: Introduction

Nearly 80% of young women living with HIV worldwide reside in sub-Saharan Africa, and new infections among young women are double that of young men in the region [1, 2]. Pregnancy is a time of biological changes that may increase HIV susceptibility [3, 4] and a period of potential sexual behavioral changes in women or their male partners that may alter HIV exposure [5]. Studies consistently show HIV incidence to be ~2-8% in African women during pregnancy and the postpartum period — an incidence rate similar to high-risk groups like female sex workers and HIV-serodiscordant couples [6-10]. In a recent systematic review involving 19 studies and 22,803 women, pooled HIV incidence was 4.7/100 person-years during pregnancy and 2.9/100 person-years postpartum [11]. Additionally, acute HIV infection among pregnant and breastfeeding women poses a double burden in sub-Saharan Africa where acute maternal HIV accounts for 26% of all mother-to-child transmissions of HIV [12, 13].

HIV prevention strategies available to women include abstinence from sexual activity, male and female condoms, and use of antiretroviral therapy (ART) by their sexual partners; however, all of these strategies depend on male partner cooperation. Tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis (PrEP) is a prevention strategy in which HIV-uninfected individuals use a daily oral antiretroviral medication as chemoprophylaxis to reduce their risk of HIV acquisition [14]. PrEP can be taken discretely without the knowledge of male partners, making it a feasible option for women who are unable to negotiate HIV prevention within partnerships. In two trials that included heterosexual women, PrEP reduced HIV acquisition in subgroups of women by 49–79% in intent-to-treat analyses, and by >85% when accounting for PrEP adherence [15, 16]. Two other trials targeting women, Vaginal and Oral Interventions to Control the Epidemic (VOICE) and PrEP Trial for HIV Prevention among African Women (FEM-PrEP), did not demonstrate an HIV prevention benefit from PrEP, but substantial evidence

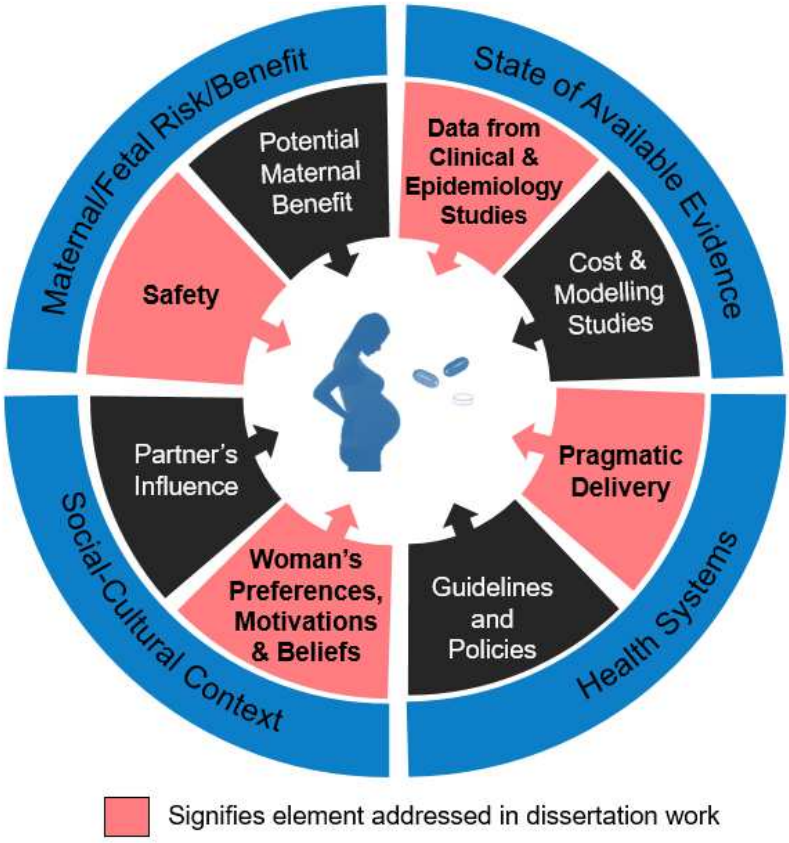
indicates those results were compromised by low adherence to the study medication [17, 18]. PrEP holds tremendous promise as a female-controlled prevention approach, and both the US Centers for Disease Control and Prevention (CDC) the World Health Organization (WHO) recommend PrEP for all individuals at substantial HIV risk (HIV incidence >3%), which includes pregnant and breastfeeding women in settings with high burden of HIV [19, 20].

For PrEP to be programmatically effective, engagement in care is required at multiple steps (i.e., seeking services, HIV testing, initiating PrEP, medication refills and adequate adherence). Opportunities exist to leverage maternal child health (MCH) systems for PrEP delivery. The public sector MCH infrastructure in many countries with high HIV burden serves most women who become pregnant and includes follow-up to 9 months postpartum for postnatal and infant care. Women are routinely offered counseling and testing for HIV in ANC clinics, which can serve as a ready platform for identifying women who would benefit from PrEP. MCH facilities are also equipped for administration of antiretrovirals [21]. The combination of substantial HIV incidence during pregnancy, increased MTCT associated with acute maternal HIV, and pre-existing widespread HIV programs within MCH systems makes this an attractive venue for PrEP implementation [22].

There are several important considerations required to translate programmatic delivery of PrEP for pregnant women into routine healthcare in clinical and policy contexts (**Figure 1**). Additional data are needed to comprehensively understand the risks and benefits of prolonged prenatal PrEP use among HIV-uninfected women. Further studies on how to identify women most likely to benefit from PrEP use during pregnancy could guide optimization of PrEP delivery in this unique population. Understanding the impact and value of pragmatic approaches for offering PrEP to pregnant women could guide scale-up of PrEP provision within clinical MCH settings.

Finally, the intra- and interpersonal context of women's lives will influence PrEP uptake and adherence and implementers will need to understand women's motivations and beliefs regarding PrEP use during pregnancy to promote PrEP utilization.

Figure 1: Considerations for programmatic delivery of PrEP for pregnant women (adapted from Beima-Sofie et al 2017)



This dissertation addresses key implementation science questions to inform broad programmatic delivery of PrEP for pregnant women. Here, we provide a brief overview of each research question.

Chapter 2: Identifying pregnant and postpartum women who may benefit from PrEP

Implementation approaches that efficiently use resources to optimize the benefit of PrEP while balancing potential concerns regarding PrEP use during pregnancy and breastfeeding have not been defined. Identification of pregnant women at the highest risk of HIV acquisition would focus PrEP counseling and provision to these women and avoid unnecessary PrEP exposure for those with no or low risk. Clinical prediction tools have been used to identify subgroups most at risk for HIV acquisition such as men who have sex with men in the United States [28, 29], HIV-serodiscordant African couples [30], and young (non-pregnant) African women. [31] Despite recognition of the importance of primary HIV prevention for pregnant and breastfeeding women, no tool has been developed to identify women most likely to acquire HIV during this critical period. The objective of this analysis was to develop a tool to identify women at highest risk for HIV acquisition during pregnancy and postpartum that could be easily implemented in MCH clinic settings.

Chapter 3: Estimated coverage of PrEP for HIV prevention among HIV-uninfected pregnant women

Targeting PrEP to individuals most at risk for HIV acquisition has been shown to yield high impact for reducing HIV incidence.[33-35] Modeling demonstrations have also found that prioritization of PrEP based on individual-level risk factors, such as being in an HIV-serodiscordant couple or having a sexually transmitted infection (STI), is a cost-effective HIV prevention strategy.[36-38]

Preventive strategies for non-HIV conditions among pregnant women have been either regionally administered or risk-guided. For example, malaria prophylaxis is recommended during pregnancy for all women residing in endemic areas, while TB prophylaxis is based on specific risk factors (such as HIV infection) within a high risk region.[39] PrEP delivery models have not incorporated subnational information on HIV prevalence to estimate the value and impact of prioritizing PrEP based on regional and/or individual-level risk of HIV acquisition for

pregnant women. We estimated the absolute number and proportion of HIV-uninfected pregnant women in Kenya who could be offered PrEP under different public health approaches, including offering PrEP universally or based on either regional HIV prevalence and/or individual-level HIV risk factors.

Chapter 4: Experiences using PrEP during pregnancy among HIV-uninfected women

The perceptions, motivations, and beliefs of HIV-uninfected women about PrEP use during pregnancy can influence its uptake and adherence. Prior to broad programmatic delivery of PrEP to pregnant women, it is important to understand motivations and beliefs for using PrEP during pregnancy to address concerns unique to this population. The personal experiences of women with direct exposure to PrEP during pregnancy offer valuable insights for informing development of effective PrEP messaging strategies and programs. We explored experiences of using PrEP during pregnancy among HIV-uninfected Kenyan women in HIV-serodiscordant couples who became pregnant while using PrEP and continued PrEP use throughout their pregnancy.

Chapter 5: Maternal tenofovir disoproxil fumarate use during pregnancy and adverse perinatal outcomes

A recent systematic review [40] that included 33 articles found no statistically significant differences between TDF use during pregnancy and comparison groups in stillbirth/pregnancy loss, preterm delivery, low birth weight, small for gestational age, birth defects, infant or maternal mortality. [101] However, the review included few prospective studies evaluating the relationship of TDF use in pregnancy and perinatal outcomes among African cohorts, and these have mixed results. [88, 102-104] Recently, the PROMISE (Promoting Maternal-Infant Survival Everywhere) study found higher rates of adverse perinatal outcomes (low birth weight, very

preterm birth, and early infant death) among HIV-infected African mothers using TDF-based ART compared to zidovudine (AZT)-based ART, however, this was in the context of protease-inhibitor-based regimens which may have been an effect modifier. [102] Other studies have not found similar associations between TDF-based vs. non-TDF-based PMTCT regimens in African cohorts. [104] We evaluated whether pregnancy loss, preterm birth and neonatal death were more frequent in a cohort of Kenyan and Ugandan HIV-infected women who used TDF-containing ART during pregnancy compared to HIV-infected women who used ART during pregnancy that did not contain TDF.

CHAPTER 2. A risk assessment tool for identifying pregnant and postpartum women who may benefit from pre-exposure prophylaxis (PrEP)

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A risk assessment tool for identifying pregnant and postpartum women who may benefit from pre-exposure prophylaxis (PrEP)

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KEY POINTS
We developed an HIV risk assessment tool for pregnant women to identify women who would most benefit from PrEP in pregnancy while minimizing unnecessary PrEP use among women at low risk.

Abstract

Background: An HIV risk assessment tool for pregnant women could identify women who would most benefit from PrEP while minimizing unnecessary PrEP exposure

Methods: Data from a prospective study of incident HIV among pregnant/postpartum women in Kenya was randomly divided into derivation (n=654) and validation (n=650) cohorts. A risk score was derived using multivariate Cox proportional hazards models and standard clinical prediction rules. Ability of the tool to predict maternal HIV acquisition was assessed using the area under the curve (AUC) and Brier score.

Results: The final risk score included the following predictors: having a male partner with unknown HIV status, number of lifetime sexual partners, syphilis, bacterial vaginosis (BV), and vaginal candidiasis. In the derivation cohort, AUC was 0.84 (95% CI 0.72-0.95) and each point increment in score was associated with a 52% (hazards ratio [HR] 1.52, 95% CI, 1.32-1.76, p<0.001) increase in HIV risk; the Brier score was 0.11. In the validation cohort, the score had similar AUC, Brier score and estimated HRs. A simplified score that excluded BV and candidiasis yielded an AUC of 0.76 (95% CI 0.67-0.85); HIV incidence was higher among women with risk scores >6 than with scores ≤6 (7.3 vs. 1.1 per 100 person-years, respectively; p<0.001). Women with simplified scores >6 accounted for 16% of the population but 56% of HIV acquisitions.

Conclusion: A combination of indicators routinely assessed in antenatal clinics was predictive of HIV risk and could be used to prioritize pregnant women for PrEP.

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Key words: HIV, pre-exposure prophylaxis, risk score, PrEP, pregnancy, postpartum

Introduction

Nearly 80% of young women living with HIV worldwide reside in sub-Saharan Africa and new infections among young women are double that of young men in the region. [1, 2] Pregnancy is a time of biological changes that may increase HIV susceptibility [3, 4] and a period of potential sexual behavioral changes in women or their male partners that may alter risk of HIV exposure. [5] In a systematic review, including 19 studies and 22,803 African women, pooled HIV incidence was 3.8/100 person-years during pregnancy and 4.7/100 person-years postpartum. [11] These maternal HIV incidence rates are similar to high-risk groups, including female sex workers and HIV-serodiscordant couples. [2, 6-11] Risk of HIV acquisition during pregnancy and postpartum translates to a substantial cumulative period of risk over the course of women's lives in sub-Saharan African regions where both fertility and HIV prevalence are high. [11] Furthermore, acute maternal HIV infection during pregnancy and breastfeeding contributes to pediatric HIV infections, especially when maternal infection is not detected and antiretrovirals are not initiated. [12, 13] Therefore, HIV prevention during pregnancy and postpartum is important for prevention of HIV in women and infants.

Current guidelines recommend pre-exposure prophylaxis (PrEP) for individuals at high risk of HIV acquisition, including women of reproductive age, and support continuation of PrEP in pregnancy for women already on PrEP. [23, 24] Few studies have evaluated PrEP use during pregnancy and breastfeeding, but available data suggest PrEP is safe during this time period. [25-27] However, implementation approaches that efficiently use resources to optimize the benefit of PrEP while balancing potential concerns regarding PrEP use during pregnancy and breastfeeding have not been defined. Identification of pregnant women at the highest risk of HIV acquisition would focus PrEP counseling and provision to these women and avoid unnecessary PrEP exposure for those with no or low risk.

Clinical prediction tools have been used to identify subgroups most at risk for HIV acquisition such as men who have sex with men in the United States [28, 29], HIV-serodiscordant African couples [30], and young (non-pregnant) African women. [31] Despite recognition of the importance of primary HIV prevention for pregnant and breastfeeding women, no tool has been developed to identify women most likely to acquire HIV during this critical period. A tool for assessing HIV risk during routine antenatal care could guide prioritization of women most likely to benefit from PrEP and other prevention strategies. The objective of this analysis was to develop a tool to identify women at highest risk for HIV acquisition during pregnancy and postpartum that could be easily implemented in maternal and child health (MCH) clinic settings.

Methods

Study participants

Data from 1,304 HIV-uninfected women in a longitudinal study of HIV incidence during and after pregnancy (the Mama Salama Study) were used to derive and internally validate a risk score for maternal HIV acquisition. The Mama Salama Study was conducted between May 2011 and July 2014 at two antenatal care (ANC) clinics in western Kenya. Recruitment, enrollment, and follow-up procedures for the parent study have been previously described. [41] Briefly, eligible pregnant women were ≥14 years old, had a negative rapid HIV test at enrollment or within the 3 months prior, planned to remain in the study area through 9 months postpartum, were willing to have a home visit, and were not enrolled in another study. Informed consent was received from all participants and the study was approved by the Kenyatta National Hospital Ethics and Research Committee and the University of Washington Institutional Review Board.

Study procedures

After enrollment, women attended follow-up visits during pregnancy (20, 24, 32, 36 weeks gestation) and postpartum (2, 6, 10, 14 weeks; 6 and 9 months). Questionnaires were administered on sociodemographic factors, reproductive history, sexual behavior, contraception and condom use, medical history, and genital symptoms. Male partner characteristics were reported by women. [41] Serial HIV nucleic acid amplification tests (NAATs) were conducted at every visit. *C. trachomatis* and *N. gonorrhoeae* were assessed at enrollment using endocervical samples for NAAT with the APTIMA Combo 2 Assay (Hologic/Gen-Probe, Inc, San Diego, CA). Syphilis serology was based on rapid plasma reagin (RPR) tests conducted at enrollment as part of routine antenatal care and abstracted from MCH booklets, or conducted by study staff if the test was not performed. All women were assessed for candidiasis, BV and *T. vaginalis* at enrollment and follow up. Candidiasis was detected by identification of budding yeast, pseudohyphae, or both on direct microscopy of a vaginal saline wet mount and KOH preparation. Vaginal Gram stained slides were evaluated using Nugent's criteria, with BV defined as a score of 7–10. *T. vaginalis* was diagnosed based on the presence of motile trichomonads on vaginal saline wet mount microscopy.

Risk score variables

The primary study outcome was incident HIV infection. All acute HIV infections detected during the study were considered incident infections. [41] In order to simulate data routinely collected during antenatal care, only enrollment variables were assessed as potential predictors. We identified potential predictors of incident maternal HIV infection based on characteristics previously assessed in the cohort: [41] demographic information (age, education, marital status, relationship duration), male partner (age, circumcision status), behavior (age of sexual debut, number of lifetime sexual partners, trading sex, condomless sex, vaginal washing and/or drying), and clinical characteristics (self-reported history of STIs, laboratory confirmed *C. trachomatis, N. gonorrhoeae, T. vaginalis,* syphilis, BV and candidiasis). In the parent study, no

HIV seroconversions occurred among women with a known HIV-infected male partner [41]; thus, knowledge of partner HIV status was dichotomized as known vs. unknown. Since laboratory testing for STIs is uncommon in most MCH settings, a separate simplified risk score was assessed that excluded STIs and genital infections except for syphilis (which is routinely assessed in antenatal care).

Statistical analysis

We used derivation and validation processes similar to previously developed risk scores for predicting HIV acquisition in other populations [29-31] that utilize methods for clinical prediction rule development and evaluation techniques described by McGinn et al [42], Moons et al [43] and Laupacis et al. [44]

Data were randomly divided into derivation (n=654) and validation (n=650) cohorts. [45, 46] Baseline differences between the derivation dataset and the validation dataset were tested using Chi-square tests for proportions and Kruskal-Wallis tests for continuous measures. In the derivation cohort, potential predictors that were associated ($p<0.10$) with incident HIV infection in univariate Cox proportional hazards models were evaluated in a multivariate model. Continuous variables were dichotomized using optimal cut-points identified through signal detection receiver operating characteristic (ROC) analyses. [47] Dichotomized variables were evaluated as predictors if measure predictability was higher using this parameterization instead of the continuous parameterization. To determine the combination of variables that best predicted incident HIV, all potential predictors from the multivariate model were assessed in a fully stepwise Cox proportional hazards model and predictors were evaluated at each step for inclusion or exclusion. We used the lowest Akaike Information Criterion (AIC) of all possible combinations of predictors from the stepwise analysis to determine the best fit model for the risk score. [48] The score values for individual risk factors were calculated by dividing the coefficients from the stepwise model for each predictor from the final stepwise model by the

lowest coefficient among all predictors and rounding to the nearest integer. [30, 31, 49] The sum of individual parameter score values for each predictor determined the final risk score for each woman. ROC analysis was used to calculate the area under the curve (AUC) with the risk score as the sole predictor of incident HIV to assess discriminative ability. [50] We also determined the Brier score to quantify how close predictions of HIV acquisition using the risk score were to the actual outcome and assess overall risk score performance. [50] Useful prediction tools have a Brier scores <0.25. [50]

The risk score was applied to the validation cohort and AUC performance and Brier score were compared with the derivation cohort. For further internal validation, average AUC of 10 different models from randomly partitioned subsets of the entire cohort was determined using a 10-fold cross-validation, a standard method of internal validation for clinical prediction tools. [42, 44] Risk scores were dichotomized into the most predictive categories using the optimal cut-point identified through ROC curves and HIV incidence was calculated by dichotomizing risk score groups in all cohorts. Analyses were repeated using the simplified risk score that excluded STIs and genital infections other than syphilis.

Results

Overall, 1304 women contributed 1235.1 person-years of follow-up and 25 incident HIV infections were detected (incidence rate 2.31 per 100 person-years). [41] The median age was 22 years and the median gestational age at enrollment was 26 weeks. Most women were married (78%) for a median of 4 years and the median years of completed education was 8. Few women reported a history of previous STIs (7%), about half (55%) reported condomless sex in the past month, and 29% had a male partner of unknown HIV status. We did not detect differences in sociodemographic, male partner, behavioral or clinical characteristics between the derivation and validation cohorts (**Table 1**).

Risk score derivation

In the derivation cohort, 14 incident infections occurred in 621.8 person-years of follow-up (incidence rate 2.3 per 100 person-years). Increased risk of HIV acquisition was associated with having a relationship duration <1 years, having a male partner of unknown HIV status, lifetime number of sexual partners, syphilis, BV, and candidiasis in univariate Cox proportional hazards models (**Table 2**). The stepwise prediction model with the lowest AIC included having a male partner of unknown HIV status, lifetime number of sexual partners, syphilis, BV, and candidiasis. Characteristics with the highest risk scores were syphilis infection and having a male partner of unknown HIV status (**Figure 2**).

When we applied the risk score to each woman and calculated individual scores, the median risk score was 4 (IQR 2-6, range 1-19). The complete risk score captured the majority of the predictive ability of the multivariate model demonstrated by nearly overlapping ROC curves (**Figure 3**). The ROC curve for the simplified risk score that excluded BV and candidiasis performed similarly but had less overlap with the multivariate model.

The AUC for the complete risk score correctly predicting HIV acquisition was 0.84 (95% CI 0.72-0.95, Table 3). Each point increment was associated with a 1.5-fold (hazards ratio [HR] 1.52, 95% CI, 1.32-1.76, p<0.001) increase in HIV risk. The optimal cut-point for most predictive categories was 7.5 for the complete risk score; HIV incidence was 13.6 per 100 person-years among women with risk scores >8 compared to 0.9 per 100 person-years among women with score $\leq$8 (p<0.001, **Figure 4A**). A complete risk score >8 had a Brier score of 0.11 and correctly identified 64% of women in the derivation cohort who acquired HIV; 11% of women had a score >8. A simplified risk score using parameters routinely available in ANC clinics, excluding BV and candidiasis, had an AUC of 0.78 (95% CI 0.65-0.92), similar to the complete risk score, and the optimal cutpoint was 6.5. There was a significant difference in HIV incidence between women with simplified scores >6 compared to those with scores $\leq$6 (8.9 per 100 person-years vs 1.0

per 100 person-years, p<0.001, **Figure 4D**). A simplified risk score >6 correctly identified 64% of women who acquired HIV in the derivation cohort; 16% of all women had a score >6. The Brier score was 0.16 when the simplified risk score was used.

Risk score validation

The risk score was applied to the validation cohort (characteristics in **Table 1**) in which 11 incident HIV infections were detected during 611.9 person-years (incidence rate 1.8 per 100 person-years). The AUC and Brier scores for both the complete and simplified risk scores in the validation cohort were similar to the derviation cohort (**Table 3**). Each point increment of the complete risk score was associated with a 1.2-fold (HR 1.21, 95% CI, 1.10-1.34, p<0.001) increase in HIV risk. HIV incidence was signficantly higher among women with complete risk scores >8 (**Figure 4B**) and women with simplified risk scores >5 (**Figure 4E**).

When applied to the overall cohort for cross-validation, the average AUC of the complete risk score for 10 subsets of data randomly selected was 0.74 (95% CI 0.62-0.87), indicating robust generalizability. The simplified score performed slightly better with cross-validation (AUC 0.76, 95% CI 0.67-0.85). The Brier scores for both risk scores were similar (Table 3).

The risk score predicted HIV acquisition better than any single risk factor: lifetime number of sexual partners (AUC 0.60, 95% CI 0.48-0.71), male partner HIV status unknown (AUC 0.63, 95% CI 0.54-0.73), syphilis (AUC 0.54, 95% CI 0.48-0.60), BV (AUC 0.63, 95% CI 0.53-0.73), and candidiasis (AUC 0.60, 95% CI 0.50-0.70).

In the overall cohort, women with complete risk scores >8 had a 6-fold increased risk of HIV (HR 6.19, 95% 2.78-13.78, p<0.001) and each point increment was associated with a 1.3-fold increased risk of HIV (HR 1.28, 95% 1.20-1.36, p<0.001). Risk of HIV associated with simplified risk scores >6 (HR 5.12, 95% CI 2.33-11.21, p<0.001) and each per point increment of simplified risk scores HR 1.31, 95% CI 1.20-1.42, p<0.001) were similar to the complete risk

score. HIV incidence was signficantly higher among women with complete risk scores >8 ($p<0.001$, **Figure 4C**) and among women with simplified risk scores >6 ($p<0.001$, **Figure 4F**) than women with lower scores. A complete risk score >8 was observed in only 10% of women, and predicted 52% of all HIV acquisitions. Simplified risk scores >6 predicted 56% of HIV acquisitions and 16% of women had scores >6.

Discussion

We derived and internally validated a risk score for HIV acquisition during pregnancy and the postpartum period using data from a large, longitudinal study designed to detect incident maternal HIV infections. We found that a composite risk score including male partner, behavioral, and clinical characteristics had good predictive ability to identify women most likely to acquire HIV. Using data that could be easily collected in standard MCH clinic settings without additional laboratory diagnostics, our simplified risk score identified 56% of pregnant women who acquired HIV while only identifying 16% of women as high risk. This risk score could identify women who would most benefit from PrEP in pregnancy and postpartum while minimizing unnecessary PrEP use among women at low risk. Our analysis contributes a unique risk assessment tool for an important subpopulation and is the first, to our knowledge, that assesses HIV risk during pregnancy and postpartum, a period of high HIV incidence with unique PrEP implementation opportunities.

Risk scores derived from serodiscordant couples have limited utility in pregnant women because 30-80% of pregnant women in sub-Saharan Africa do not know the HIV status of their partner. [30, 51-57] Risk scores derived from non-pregnant ‘high risk’ women, such as those in the VOICE study also have limited relevance to pregnant women because these are predominantly unmarried women counseled to not become pregnant who frequently (>90%)

used hormonal contraception. [17] The discriminatory ability of a risk score in pregnancy is also of importance to limit unnecessary fetal drug exposure for women at no or low risk of HIV.

We found that syphilis infection and having a male partner with unknown HIV status were highly predictive of HIV acquisition and were sufficiently predictive for inclusion in the simple risk score. This is consistent with previous studies that have found knowledge of male partners' HSV-2 and HIV status are associated with lower acquisition risk for women due to adoption of preventive behaviors following disclosure. [58, 59] Syphilis infection is a known risk factor for HIV. [60] Importantly, these two variables can be rapidly assessed in routine MCH settings to discriminate women who could benefit from PrEP.

Pregnancy and the postpartum period are attractive for PrEP implementation. Attendance at MCH visits for antenatal care and infant immunizations is high in sub-Saharan Africa. Women are universally offered counseling and testing for HIV in antenatal clinics, which can serve as a platform for identifying women who would benefit from PrEP. The combination of substantial maternal HIV incidence, increased mother-to-child HIV transmission associated with acute maternal HIV infection, and HIV testing infrastructure makes this a critical and feasible period for PrEP implementation. Previous studies suggest that targeting PrEP to individuals most at risk for HIV acquisition yields high impact for reducing HIV incidence. [34, 36-38, 61, 62] In our study, simplified risk scores >5 were associated with a nearly 5-fold increased risk of HIV acqusition. A simple risk assessment tool would allow clinicians to rapidly identify women most likely to benefit from targeted HIV prevention, including PrEP. Prior to widespread PrEP implementation for pregnant and postpartum women, adherence and safety of PrEP in this population should be considered. [17, 18, 63-65]

Our study has limitations. Data from other settings are needed to externally validate the risk score. [43, 66, 67] Some known cofactors for HIV acquisition, such as HSV-2, were not included in our models because the parent study did not evaluate them. [68] In addition, the number of incident maternal HIV infections was smaller than other derivation cohorts. [29-31] However, other risk prediction tools [69, 70] have successfully used a similar number of incident events and statistical modeling demonstrations have shown that AUC estimations are minimally affected by sample size. [71] Despite the relatively small number of incident HIV infections, our risk assessment tool predicted HIV acquisition well with an AUC of 0.74, similar to HIV risk scores developed with larger sample sizes (AUC ranging 0.67-0.74). [28-31]

Conclusion

We found that a combination of characteristics routinely assessed during ANC, yielded high predictive utility for HIV risk in pregnant and postpartum women. Targeting PrEP for women at high risk of HIV acquisition could have substantial impact on maternal and infant HIV incidence, limit unnecessary PrEP exposure to women at low risk, and use resources efficiently.

CONFLICTS OF INTEREST

RSM receives research funding, paid to the University of Washington, from Hologic Corporation. All other authors declare that no competing interests exist.

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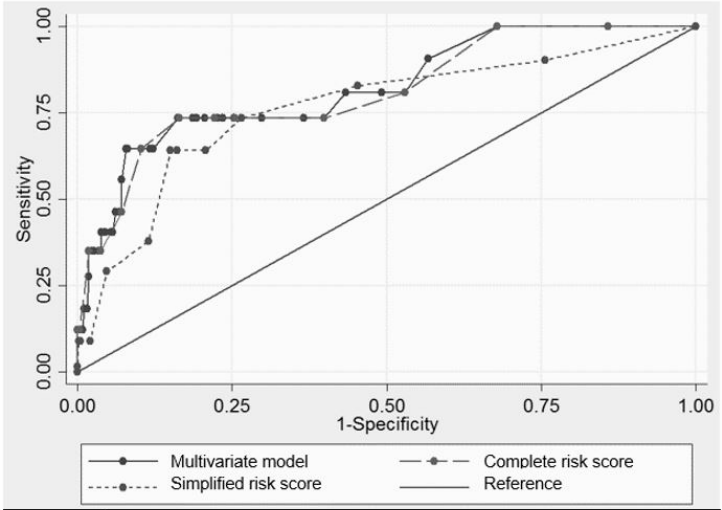
Figures

Figure 2. Risk assessment tool score card for antenatal care clients

Risk factor	Value per factor	Complete score	Simplified score
No. of lifetime sexual partner			
1 point per sexual partner	Enter at least 1		
Male partner HIV status			
Known or no male partner	0		
Unknown	6		
Syphilis			
RPR nonreactive	0		
RPR reactive	5		
Bacterial vaginosis			
Negative or not screened	0		
Positive	2		
Candidiasis			
Negative or not screened	0		
Positive	3		
	Total risk score		

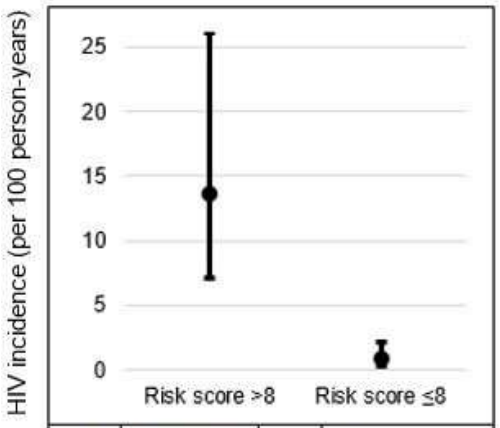
Figure 3. ROC curve and cut points of risk score in derivation cohort



	Sensitivity and Specificity of the Complete Risk Score at Different Score Cuts							
	≥3	≥4	≥5	≥6	≥7	≥8	≥9	≥10
Sensitivity	100%	86%	79%	79%	79%	79%	64%	50%
Specificity	33%	48%	61%	75%	78%	84%	90%	93%

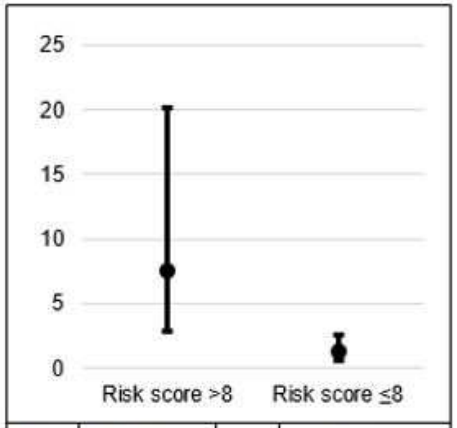
Figure 4. Incidence of HIV (per 100 person-years) by risk score category

A. Complete risk score (derivation cohort)



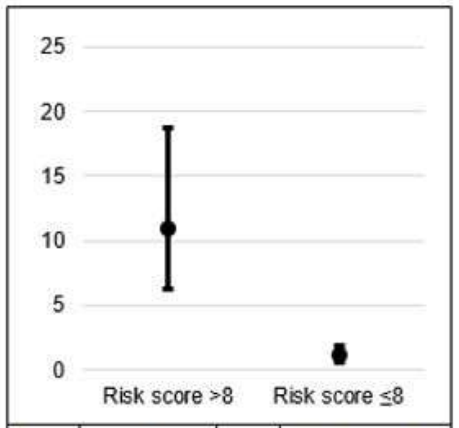
Risk score	No. HIV acquisitions	N	Incidence (95% CI)
>8	9	75	13.6 (7.1-26.1)
≤8	5	579	0.9 (0.4-2.2)

B. Complete risk score (validation cohort)



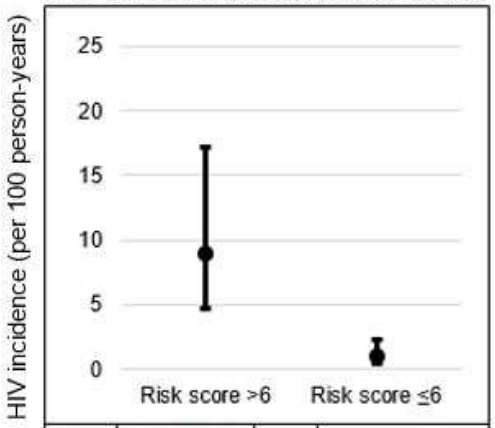
Risk score	No. HIV acquisitions	N	Incidence (95% CI)
>8	4	58	7.6 (2.8-20.2)
≤8	7	592	1.3 (0.6-2.6)

C. Complete risk score (full cohort)



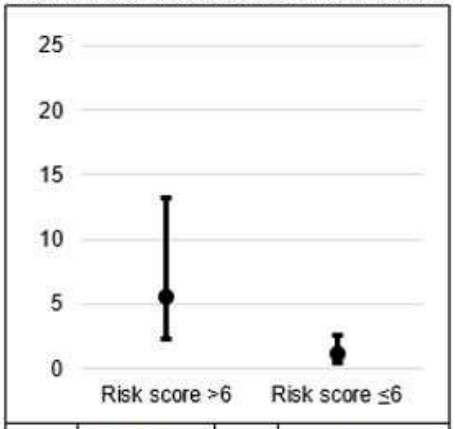
Risk score	No. HIV acquisitions	N	Incidence (95% CI)
>8	13	133	10.9 (6.3-18.8)
≤8	12	1171	1.1 (0.6-1.9)

D. Simplified risk score (derivation cohort)



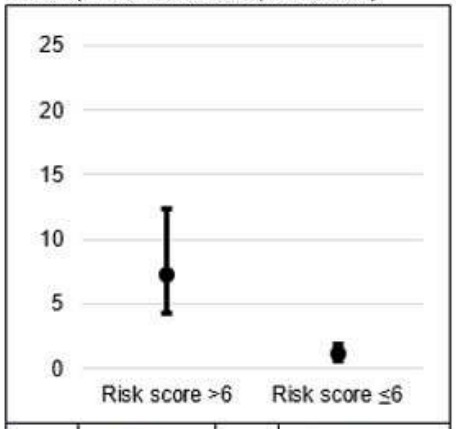
Risk score	No. HIV acquisitions	N	Incidence (95% CI)
>6	9	107	8.9 (4.7-17.2)
≤6	5	547	1.0 (0.4-2.3)

E. Simplified risk score (validation cohort)



Risk score	No. HIV acquisitions	N	Incidence (95% CI)
>6	5	97	5.5 (2.3-13.2)
≤6	6	553	1.1 (0.5-2.6)

F. Simplified risk score (full cohort)



Risk score	No. HIV acquisitions	N	Incidence (95% CI)
>6	14	204	7.3 (4.3-12.3)
≤6	11	1100	1.1 (0.6-1.9)

	N (%) of Median (IQR)		p-value[1]
	Derivation cohort (n=654)	Validation cohort (n=650)	
Demographic characteristics			
Age (years)	22 (19-26)	22 (19-27)	0.24
Education (years)	8 (8-10)	8 (7-11)	0.92
Married	507 (79%)	516 (78%)	0.41
Polygamous relationship[2]	70 (11%)	88 (14%)	0.12
Relationship duration (years)[3]	4 (1-7)	4 (1-9)	0.63
Partner characteristics			
Partner age difference (years older)[3]	5 (3-8)	5 (4-9)	0.51
Partner uncircumcised[3,4]	405 (69%)	403 (69%)	0.76
Partner HIV status[3,4]			

Table 1. Baseline characteristics of derivation and validation cohorts

Negative	429 (72%)	413 (69%)	0.51
Positive	10 (1%)	8 (1%)	0.73
Unknown[5]	161 (27%)	180 (30%)	0.58
Sexual behavior and practices			
Age at sexual debut (years)	16 (15-18)	16 (15-18)	0.30
Lifetime number of sexual partners	2 (1-3)	2 (2-3)	0.12
History of trading sex	62 (9%)	72 (11%)	0.35
Any condomless sex in the past month	350 (55%)	359 (56%)	0.61
Any vaginal washing in the past week	389 (59%)	392 (60%)	0.76
Any vaginal drying in the past week	126 (19%)	107 (16%)	0.19
STIs and genital tract infections			
History of STIs[4]	42 (6%)	45 (7%)	0.80
C. trachomatis	44 (7%)	28 (4%)	0.05
N. gonorrhoeae	14 (2%)	19 (3%)	0.37
T. vaginalis	39 (6%)	43 (7%)	0.62
Syphilis	7 (1%)	6 (1%)	0.79
Bacterial vaginosis	158 (24%)	143 (22%)	0.36
Candidiasis	160 (24%)	167 (26%)	0.60

[1]Chi-squared test for proportions or Kruskal-Wallis for continuous measures
[2]Among married women
[3]Among women with a current male partners
[4]Self-reported by women
[5]Includes male partners that have not been tested for HIV

Table 2. Analysis of predictors and calculation of risk score in the derivation cohort

Enrollment characteristic	Univariate		Multivariate[1]		Stepwise[2]			Risk score[3]
	Crude HR	p-value	Adjusted HR[2]	p-value	Adjusted HR[2]	p-value	Regression coefficient	
Demographic Characteristics								
Age <21 years[4]	1.22 (0.42-3.52)	0.710						
Education <8 years[4]	0.83 (0.23-2.98)	0.778						
Married	0.74 (0.23-2.36)	0.610						
Polygamous relationship	2.42 (0.67-8.67)	0.176						
Marriage duration <1 year[4]	3.00 (0.94-9.59)	0.063	2.60 (0.74-9.17)	0.136				
Partner Characteristics								
Partner age difference (years older)[4]	1.06 (0.98-1.16)	0.158						
Partner uncircumcised[5]	1.31 (0.35-4.84)	0.686						
Partner HIV status unknown	5.84 (2.05-16.65)	0.001	10.75 (3.13-36.94)	<0.001	11.53 (3.39-39.26)	<0.001	2.45	6
Sexual Behavior and Practices								
Age at sexual debut < 17 years[4]	2.06 (0.69-6.14)	0.196						
Lifetime number of sexual partners[4]	1.40 (1.18-1.67)	<0.001	1.44 (1.20-1.75)	<0.001	1.50 (1.23-1.82)	<0.001	0.41	1
History of trading sex	1.57 (0.35-7.02)	0.554						
Any condomless sex in the past month	0.82 (0.29-2.34)	0.714						
Any vaginal washing in the past week	1.22 (0.41-3.64)	0.722						
Any vaginal drying in the past week	1.64 (0.52-5.24)	0.401						
STIs and Genital Tract Infections								
History of STIs[5]	2.38 (0.53-10.65)	0.255						
C. trachomatis	1.15 (0.15-8.83)	0.895						
Syphilis	6.72 (0.87-51.78)	0.067	10.80 (1.29-90.50)	0.028	9.05 (1.11-73.95)	0.040	2.20	5
Bacterial vaginosis	4.29 (1.49-12.36)	0.007	2.59 (0.82-8.21)	0.104	2.61 (0.83-8.17)	0.099	0.96	2
Candidiasis	3.11 (1.09-8.87)	0.034	3.54 (1.09-11.51)	0.036	3.51 (1.08-11.37)	0.037	1.25	3

[1]Covariates selected for multivariate analysis were based on factors associated with HIV infection ($p<0.10$) in univariate analysis
[2]Covariates selected for the stepwise multivariate model based on lowest Akaike Information Criterion (AIC) score from stepwise procedure
[3]Points were assigned to each risk factor by dividing each coefficient from the stepwise proportional hazard model by 0.41 (the lowest coefficient value, corresponding to lifetime number of sexual partners) and rounding to the nearest integer
[4]Continuous variables were dichotomized using optimal cut-points identified through signal detection receiver operating characteristic (ROC) analyses. Dichotomized variables were evaluated as predictors if measure predictability was higher using this parameterization instead of the continuous parameterization.
[5]Self-reported by women

Table 3. Discrimination performance of complete and simplified risk score

	Complete risk score[1]			Simplified risk score[2]		
Cohort	**Derivation**	**Validation**	**Overall[3]**	**Derivation**	**Validation**	**Overall[3]**
Proportion of women with high risk score (%)[4]						
All women	11%	9%	10%	16%	15%	16%
HIV-seroconverters	64%	36%	52%	64%	45%	56%
Discrimination performance						
AUC (95% CI)	0.84 (0.72-0.95)	0.73 (0.57-0.90)	0.74 (0.62-0.87)	0.78 (0.65-0.92)	0.72 (0.58-0.87)	0.76 (0.67-0.85)
Brier score	0.11	0.09	0.10	0.16	0.15	0.15

AUC = area under the receiver operating characteristic curve

[1] Complete risk score includes having a male partner with unknown HIV status, lifetime number of sexual partners, syphilis, bacterial vaginosis and vaginal candidiasis

[2] Simplified risk score excludes bacterial vaginosis and vaginal candidiasis

[3] AUC for the overall cohort was calculated as the average AUC of 10 subsets of data randomly selected from the overall cohort

[4] High risk scores defined as score >8 for the complete risk score and >6 for the simplified risk score excluding BV and candidiasis based on optimal cut-points in ROC analysis

CHAPTER 3. Estimated coverage of pre-exposure prophylaxis for HIV prevention among HIV-uninfected pregnant women using risk-based versus regional prevalence approaches

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Brief Report: Estimated coverage of pre-exposure prophylaxis for HIV prevention among HIV-uninfected pregnant women using risk-based versus regional prevalence approaches

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Conflicts of interest: The authors declare that no conflicts of interest exist.

Word count: 2322 (limit 2000 with 2 tables/figures)

Abstract

Objective: Pre-exposure prophylaxis (PrEP) could prevent HIV in pregnancy and postpartum, though implementation strategies are undefined. We estimated the absolute number and proportion of HIV-uninfected pregnant women in Kenya who could be offered PrEP under different public health approaches, including offering PrEP universally or based on either regional HIV prevalence and/or individual-level HIV risk factors.

Methods: Register data from 62 antenatal (ANC) facilities throughout Kenya were systematically abstracted (first 10% of visits per facility per year; 2011-2013). Potential high HIV risk was defined as having syphilis and/or a male partner of unknown or HIV-positive status. Kenya Demographic and Health Survey 2014 data were used to project national estimates.

Results: Of 8,634 women with abstracted ANC data, partner HIV status and syphilis data were available for 85% and 69%, respectively. Median age at first ANC was 24 years, 18% were <20 years, 86% were married; 1% had syphilis. Couples HIV testing was low (3%) and 54% of women reported not knowing partner's HIV status. Overall, 39% of women had potential high HIV risk; higher in Nyanza (51%) than other regions (Prevalence Ratio=1.5, 95% CI 1.1-2.2). Offering PrEP to all pregnant women nationally would result in 61% of PrEP provision to women with low HIV risk. Offering PrEP only to pregnant women in the region with highest HIV prevalence (Nyanza) would reduce PrEP use among low-risk women by 74%, but exclude 63% of high-risk women nationally.

Conclusions: Many pregnant women are unaware of partner HIV status. Combined prevalence and risk assessment strategies may be useful to strategically deliver PrEP in pregnancy.

Word count: 259 (limit 250)

Introduction

Women in high HIV prevalence regions of sub-Saharan Africa have substantial risk of acquiring HIV during and soon after pregnancy.[3, 4, 11] An estimated one-third of all mother-to-child transmission of HIV (MTCT) is due to acute maternal HIV infection during pregnancy and breastfeeding.[12, 13, 72] To reach global targets for elimination of MTCT and HIV prevention for mothers, it is critical to integrate effective primary HIV prevention strategies into maternal and child health (MCH) services. Pre-exposure prophylaxis (PrEP) decreases HIV risk in adherent women.[18, 73-76] The World Health Organization (WHO) recommend PrEP for individuals at substantial HIV risk (HIV incidence >3%), including pregnant and breastfeeding women in high-burden settings.[19, 20] Programmatic delivery of PrEP for pregnant women is currently being considered in high-prevalence regions[32], though implementation approaches that efficiently optimize the benefit of PrEP during pregnancy have not been defined.

Prioritizing women at high-risk for HIV acquisition during pregnancy could focus PrEP counseling and provision while avoiding unnecessary PrEP use for women with low HIV risk. Targeting PrEP to individuals most at risk for HIV acquisition has been shown to yield high impact for reducing HIV incidence.[33-35] Modeling demonstrations have also found that prioritization of PrEP based on individual-level risk factors, such as being in an HIV-serodiscordant couple or having a sexually transmitted infection (STI), is a cost-effective HIV prevention strategy.[36-38] Similarly, preventive strategies for non-HIV conditions among pregnant women have been either regionally administered or risk-guided. For example, malaria prophylaxis is recommended during pregnancy for all women residing in endemic areas, while TB prophylaxis is based on specific risk factors (such as HIV infection) within a high risk region.[39] PrEP delivery models have not incorporated subnational information on HIV

prevalence to estimate the value and impact of prioritizing PrEP based on regional and/or individual-level risk of HIV acquisition for pregnant women.

We estimated the absolute number and proportion of HIV-uninfected pregnant women in Kenya who could be offered PrEP under different public health approaches, including offering PrEP universally or based on either regional HIV prevalence and/or individual-level HIV risk factors.

Methods

We conducted a secondary analysis using data from a large cross-sectional survey of antenatal (ANC) registers. Data were abstracted for the period of January 2011 to December 2013. The primary aim of the parent survey was to assess national-level coverage of prevention of MTCT services among ANC attendees and HIV-exposed infants enrolled in care in randomly selected facilities across Kenya.[77]

Sampling Design

The sampling frame included all facilities providing routine PMTCT services with ≥100 annual HIV-infected ANC clients as reported to the Kenya National AIDS and STI Control Program (NASCOP). Facilities were randomly selected for inclusion, stratified by facility size defined as: small (100-150 annual HIV-infected ANC clients), medium (151-250 annual HIV-infected ANC clients), and large (≥251 annual HIV-infected ANC clients). The number of facilities selected in each strata was proportional to the number of facilities within each strata in the overall sampling frame (65% small, 25% medium and 10% large). Stratified random sampling was used to select 62 facilities from the 92 facilities in the overall sampling frame: 40 small, 16 medium and 6 large. Selected facilities were from the regions of Nyanza, Nairobi, Coast, Rift Valley and Eastern.

Data from the first 10% of all ANC visits occurring from January to December were included for each year from 2011 to 2013. Records that did not include visit date and/or whether the record

was from an initial or repeat ANC visit were excluded. Only records from first ANC visits were included in the final study population.

Data abstraction

Study staff abstracted data from standardized Ministry of Health paper-based ANC registers. Study staff scanned each page for the study period with identifying information blocked with an opaque cover. Data from electronic images of register pages were digitized using Captricity©, a proprietary cloud-based data transcription service that uses a combination of computer algorithms and manual checks to digitize hand-written data. Image capture and digitization were piloted using 100 register pages prior to study implementation to ensure accuracy and consistency between paper-based and digitized data.

Definition of variables

We stratified public health approaches for offering PrEP to pregnant women based on individual-level potential HIV risk and regional HIV prevalence. We defined potential high HIV risk (based on individual-level characteristics) as having syphilis (documentation rapid plasma reagin [RPR] positive results) and/or having a partner of unknown or positive HIV status. These characteristics were selected based on the availability of indicators in the ANC registries, previous studies which identified these characteristics as risk factors for HIV acquisition among pregnant women in Kenya[78], and current Kenya Ministry of Health PrEP recommendations.[32] Unnecessary PrEP use was defined as women hypothetically offered PrEP without potential high risk for HIV based on individual-level characteristics (i.e. documented as syphilis-negative and having an HIV-uninfected partner). Nyanza was defined as the region with highest HIV prevalence based on its overall adult HIV prevalence of 15.1%, according to the latest Kenya AIDS Impact Survey 2014 (all other regions have <5% HIV

prevalence).[79] Other variables were defined per Kenya Ministry of Health-issued ANC registry-specified classifications.

Statistical Analyses

Demographic and clinical characteristics were summarized with medians for continuous measures and proportions for categorical variables. The proportion of women with potential high HIV risk based on individual-level characteristics was estimated nationally and by region. We estimated the absolute number and proportion of HIV-uninfected pregnant women in Kenya who could be offered PrEP under four different public health approaches, including offering PrEP to: 1) all HIV-uninfected pregnant universally, 2) only HIV-uninfected pregnant women with potential high HIV risk based on individual characteristics, 3) only pregnant women in the region with highest HIV prevalence, and 4) only pregnant women with potential high HIV risk based on individual characteristics within the region with highest HIV prevalence . We multiplied the total number of pregnant women nationally according to Kenya Demographic and Health Survey (KDHS) 2014 (1.53 million) by the proportion of women in Eastern, Coast, Rift Valley, Nairobi and Nyanza regions (74%) to estimate the number of pregnant women for all regions that contributed data to our study.[80] The number of pregnant women with potential high HIV risk based on individual-level characteristics was estimated by multiplying the total number of pregnant women in all regions by the proportion with syphilis and/or a partner of unknown or positive HIV status. The number of pregnant women in Nyanza was estimated by multiplying the total number of pregnant women nationwide (1.53 million) by the proportion in Nyanza (26%). The number in Nyanza with potential high risk for HIV was estimated by multiplying the total number of pregnant women in Nyanza by the proportion with syphilis and/or a partner of unknown or positive HIV status within Nyanza. All analyses were weighted to account for the complex sampling design, including clustering at the clinic-level. Statistical significance was based on a 2-sided p-value of <0.05. Analyses were performed using STATA 13.

Ethical considerations

Ethical approval was obtained from the ethical review committees at the Kenya Medical Research Institute (KEMRI), the University of Washington (UW), and the US Centers for Disease Control and Prevention (CDC).

Results

Overall, 8,634 ANC attendees (93% of all abstracted records) were HIV-uninfected and had data available on syphilis and/or partner HIV status. The regional distribution of ANC attendees was: Eastern 1,127 (13.1%), Rift Valley 1,284 (14.9%), Coast 1,362 (16.2%), Nairobi 1,619 (18.8%), and Nyanza 3,208 (37.2%). The median age of ANC attendees was 24 years, 18% were <20 years, most were married (86%) and 37% were pregnant for the first time.

Syphilis testing results were available for 69% of ANC attendees and among those with results, 1% were RPR positive. Data on male partner HIV status was available for 85% of ANC attendees of which nearly half (54%) had documentation of unknown male partner HIV status. Only 3% had HIV tested as a couple and 1% reported knowing their male partner was HIV-infected. Overall, 39% of women had either documentation of syphilis infection and/or a partner of positive or unknown HIV status, which defined potential high HIV risk in our study. Regions with prevalence of pregnant women with high HIV risk ≥30% overlapped with higher general population HIV prevalence (**Figure 5**). Prevalence of pregnant women with high HIV risk was highest in Nyanza (51%) than other regions (Prevalence Ratio 1.5, 95% CI 1.1-2.2, p=0.04, Figure 1A). In all other regions, <40% of women had potential high HIV risk: Nairobi (38%), Rift Valley (33%), Coast (32%), and Eastern (28%).

A universal approach for offering PrEP nation-wide would result in 100% PrEP coverage among pregnant women with high HIV risk, but 61% of pregnant women offered PrEP would not be categorized as high HIV risk based on their individual-level characteristics (**Figure 6**). A

prevalence-based approach, offering PrEP to all pregnant women in Nyanza only, would reduce the national proportion of low risk pregnant women who would be offered PrEP to 13%. However, under this approach, less than half of pregnant women with high HIV risk nationally would be offered PrEP. Restricting PrEP delivery to only high HIV risk women in Nyanza would maintain coverage levels for those who may benefit from PrEP while reducing use among women with low HIV risk in the region.

We repeated the analyses to estimate the absolute numbers of pregnant women in each of the approaches for offering PrEP. Using a universal approach, over 1.1 million pregnant women would be offered PrEP, approximately 688,000 of whom would be considered low risk based on individual-level characteristics (**Figure 6**). When restricting delivery to Nyanza, the number of pregnant women offered PrEP would be reduced to 295,000. Restricting PrEP delivery in Nyanza to only pregnant women with potential high HIV risk would further reduce the number of women offered PrEP overall and among those with low HIV risk.

Discussion

Our study is the first to estimate the proportion and number of HIV-uninfected pregnant women who could be offered PrEP in Kenya under pragmatic delivery scenarios. In this large survey, high HIV risk was common, based on routinely collected ANC indicators, and varied by region. We found that a national or regional approach for offering PrEP that incorporates individual-level HIV risk assessment would decrease the number of women offered PrEP who have low HIV risk while providing PrEP to those likely to benefit. The combination of substantial HIV incidence during pregnancy, increased MTCT associated with acute maternal HIV, and pre-existing widespread HIV programs within MCH systems makes this setting an attractive opportunity for PrEP implementation.[22] Future approaches that include information on regional HIV prevalence within a risk assessment may further improve PrEP delivery for pregnant women.

Reaching efficient PrEP implementation for pregnant women will require clearly defined strategies for intervention delivery. Efficient scale-up will depend on increased patient and provider knowledge of PrEP, as well as increased accessibility of PrEP drugs to those identified as most at risk for HIV acquisition. Particularly in settings that have fewer financial resources, optimized PrEP strategies can be of great additional value from both a public health and economic perspective. A modeling demonstration among all adults from one community in Zambia found that PrEP is a cost-effective prevention method, averting 31% of HIV infections over 10 years at $323 per quality-adjusted life-year (QALY), when prioritized to those most at risk for HIV.[36] In our study, potential high HIV risk based on individual-level characteristics varied from 28-51% across regions, signally that incorporating regional information may be important for planning delivery approaches. Future mathematical models that specifically evaluate prioritization of PrEP for pregnant women are needed to understand the cost-effectiveness of prioritizing PrEP within this unique population.

Current guidelines in Kenya recommend PrEP for individuals who recently had an STI and/or have sex partners of positive or unknown HIV status.[32] Previous studies found that having a male partner of unknown HIV status was associated with a >5-fold increased risk for HIV acquisition among pregnant women in Kenya. [78] Less than 5% of ANC attendees in our study tested for HIV as a couple with their partners and over half did not know their partner's HIV status. Accurate partner HIV status information is key to preventing new HIV infections in pregnant women and to targeting effective prevention strategies to women at highest risk.[81, 82] ANC clinics routinely screen for syphilis, which was previously associated with a 9-fold increased incidence of HIV among pregnant women.[83] In our study, nearly one-third of ANC attendees were missing syphilis results. Interventions to increase partner HIV testing and ensure syphilis screening during ANC are needed to refine provision of PrEP for pregnant women. [84]

Our study has limitations. We abstracted data from ANC registries that were initially completed for non-research purposes. Therefore, an appreciable proportion of ANC attendees were missing key indicators and records missing both syphilis and male partner HIV status data were excluded. Our study only included records from first ANC visits and therefore syphilis testing could have been performed subsequently at later visits. Male partner HIV status was largely self-reported by women as few women tested as couple with their partner. It is likely that the frequency of HIV-serodiscordance would be higher if male partner status was confirmed with HIV testing. We collected data cross-sectionally and cannot determine if women classified as having potential high HIV risk acquired HIV, though the indicators we used were from a published HIV risk score for pregnant Kenyan women.[78] This analysis does not include mathematical modeling or cost-effectiveness analyses. However, our findings are useful to start to develop conceptual models for PrEP delivery in pregnancy and to inform parameterization in more comprehensive models of different PrEP delivery approaches for this population.

In conclusion, strategies that combine HIV prevalence and individual-level risk assessment may be useful for offering PrEP in pregnancy. Many pregnant women remain unaware of their partner's HIV status and few test for HIV as a couple. Enhancing partner HIV testing could improve PrEP provision by refining identification of women who could benefit from PrEP.

Figure 5. Frequency of potential high HIV risk among pregnant women and adult HIV prevalence (KAIS 2012) [79], by region

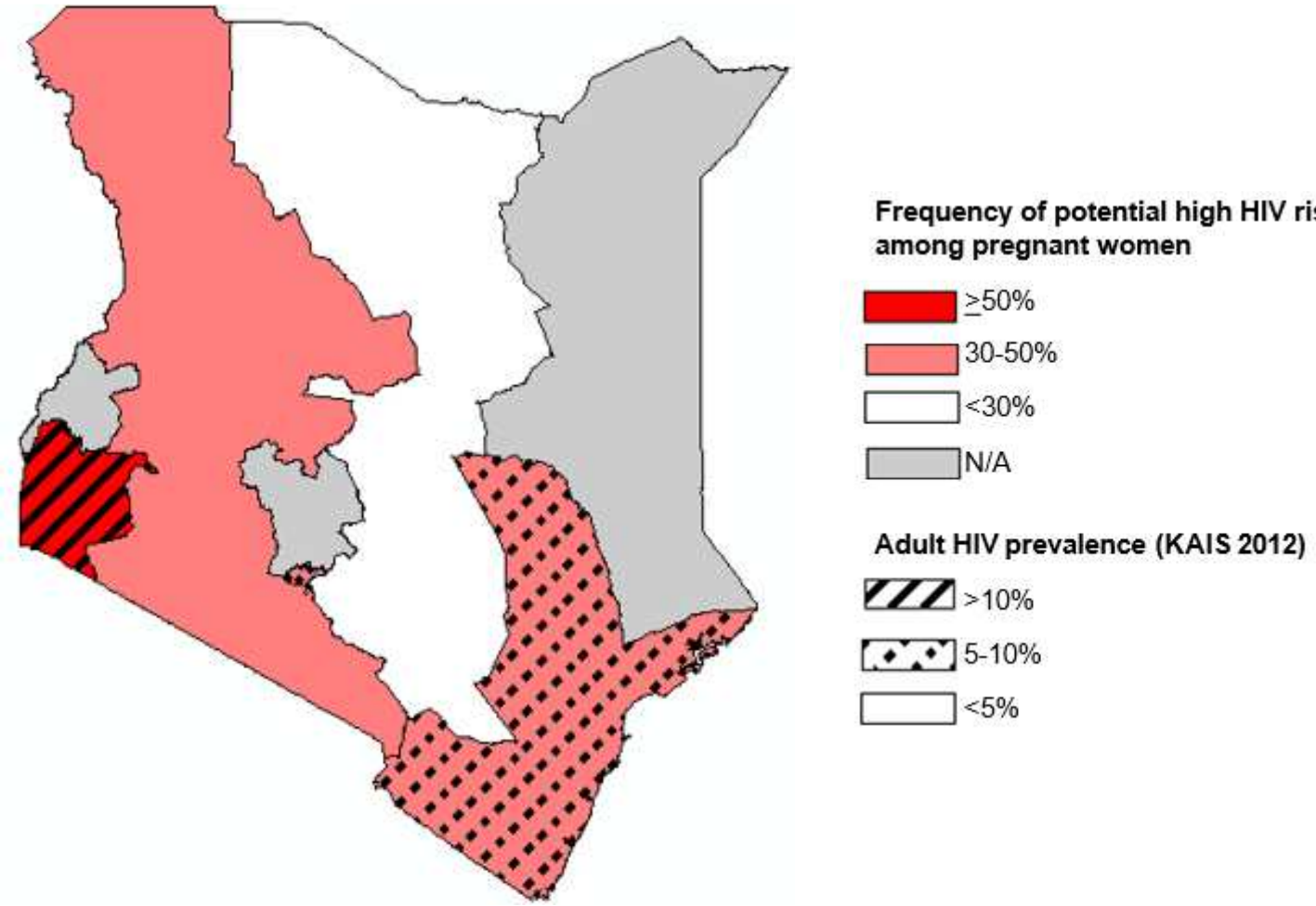
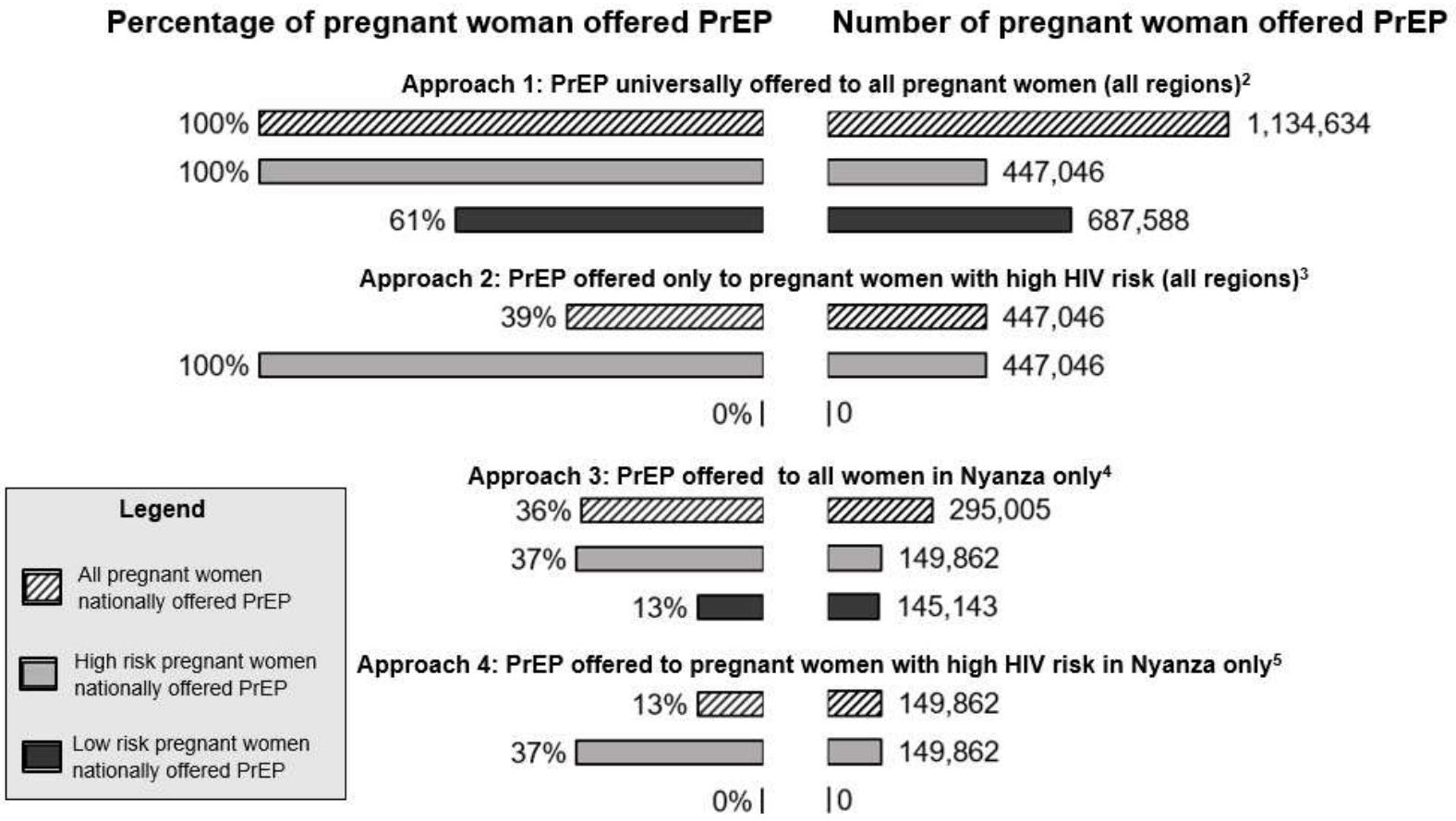


Figure 6. PrEP coverage by public health approach for offering PrEP



[1] Low risk women were defined as ANC clients offered PrEP who are were syphilis-negative and had a known HIV-uninfected male partner

[2] The number of pregnant women for all regions was estimated by multiplying the total number of pregnant women nationally (1.53 million, KDHS 2014) by the proportion of women in Eastern, Coast, Rift Valley, Nairobi and Nyanza regions (74%, KDHS 2014).

[3] The number of pregnant women with high HIV risk was estimated by multiplying the total number of pregnant women in all regions by the proportion with high HIV risk (39%).

[4] No. of pregnant women in Nyanza was estimated by multiplying the total no. of pregnant women nationwide (1.53 million, KDHS 2014) by the proportion of women in Nyanza (26%)

[5] No. of pregnant women in Nyanza with high risk for HIV was estimated by multiplying the total no. of pregnant women in Nyanza by the proportion with high HIV risk in Nyanza

CHAPTER 4: "*I did not want to give birth to a child who has HIV*": Experiences using PrEP during pregnancy among HIV-uninfected Kenyan women in HIV-serodiscordant couples

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"*I did not want to give birth to a child who has HIV*": Experiences using PrEP during pregnancy among HIV-uninfected Kenyan women in HIV-serodiscordant couples

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Word count: 3364 (word limit 3500)

Running head: Experiences of using PrEP during pregnancy (37 characters, limit 40)

Abstract

Objectives
The perceptions, motivations, and beliefs of HIV-uninfected women about PrEP use during pregnancy can influence its uptake and adherence. This study elicited the views of HIV-uninfected women with personal experience taking PrEP during pregnancy.

Design
Qualitative interviews were conducted with HIV-uninfected women who had personal experience taking PrEP while pregnant.

Methods
Semi-structured interviews were conducted with 21 HIV-uninfected Kenyan women in HIV-serodiscordant couples enrolled in an open-label PrEP demonstration project who became pregnant while using PrEP and continued PrEP through their pregnancy. Interviews were audio-recorded and transcribed into English. A qualitative descriptive analysis was performed, using a constant comparison approach to identify key themes related to PrEP use in pregnancy.

Results
Desire to remain HIV-uninfected and have an HIV-free infant were the strongest motivators influencing continued use of PrEP during pregnancy. Supporting HIV-infected partners and childbearing within an HIV-serodiscordant relationship were also motivators. Women had challenges distinguishing normal pregnancy symptoms from PrEP side effects and were concerned that observed side effects could be signs of danger for the infant related to PrEP exposure. Healthcare providers were important conduits of knowledge about PrEP, and continuity of PrEP providers throughout pregnancy facilitated adherence.

Conclusions
HIV-uninfected women in HIV-serodiscordant couples were motivated to use PrEP during pregnancy to remain HIV-uninfected and to have an HIV-free child, but had concerns about side effects. Healthcare providers will be important for PrEP messaging and adherence support in this unique population.

Word count: 235 (limit 250)

Key words:
Obstetrics / gynecology; PrEP; Women; Africa; Qualitative data; Prevention of mother to child transmission / vertical transmission; Prevention of sexual transmission

Introduction

Women in high HIV prevalence regions of sub-Saharan Africa have substantial risk of acquiring HIV during and soon after pregnancy [3, 4, 11]. Pregnant women who become acutely infected with HIV are estimated to account for 26% of all mother-to-child HIV transmissions (MTCT) in high HIV prevalence settings [12, 13]. Pre-exposure prophylaxis (PrEP) decreases HIV incidence in adherent women [18, 73-76]. Both the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend PrEP for individuals at substantial HIV risk (HIV incidence >3%), which includes pregnant and breastfeeding women in high-burden settings [19, 20]. Several individual studies [25, 85-89] and one systematic review [40] concluded that there is no safety-related rationale for prohibiting PrEP during pregnancy and breastfeeding. Clinical guidelines from the CDC suggest continuing PrEP for women in HIV-serodiscordant partnerships who become pregnant or in those who do not know the HIV status of their male partner [20]. Programmatic delivery of PrEP for pregnant women is currently being considered in high-prevalence regions [32].

PrEP programmatic implementation involves awareness regarding PrEP, HIV testing, PrEP initiation, retention, and adherence, and routine monitoring. Opportunities exist to leverage existing maternal child health (MCH) systems for PrEP delivery. Public-sector MCH clinic infrastructure in many countries with high HIV burden serves most women who become pregnant and includes frequent follow-up postpartum. Women are routinely offered HIV testing in antenatal clinics, which can identify women who would benefit from PrEP. MCH facilities are also equipped for administration of antiretrovirals, giving staff experience counseling about potential side effects and adherence to antiretrovirals [21]. The combination of substantial HIV incidence during pregnancy, increased MTCT associated with acute maternal HIV, and pre-existing widespread HIV programs within MCH systems makes this an attractive venue for PrEP implementation [22].

Prior to broad programmatic delivery of PrEP to pregnant women, it is important to understand motivations and beliefs for using PrEP during pregnancy to address concerns unique to this population. The personal experiences of women with direct exposure to PrEP during pregnancy offer valuable insights for informing development of effective PrEP messaging strategies and programs. We explored experiences of using PrEP during pregnancy among HIV-uninfected Kenyan women in HIV-serodiscordant couples who became pregnant while using PrEP and continued PrEP use throughout their pregnancy.

Methods

Study design and Population

From July 2015-March 2016, we conducted individual interviews with HIV-uninfected women in heterosexual HIV-serodiscordant couples participating in the Partners Demonstration Project at the Thika and Kisumu, Kenya sites. The Partners Demonstration Project is a recently completed open-label implementation project evaluating integrated delivery of PrEP and ART for HIV prevention among 1013 high risk HIV serodiscordant couples at 4 sites in Kenya and Uganda [51, 90]. Recruitment and procedures of the parent study have been previously described [90]. Briefly, PrEP was recommended for HIV-uninfected partners until HIV-infected partners initiated and sustained antiretroviral therapy (ART) use for at least 6 months. All participants were members of a mutually-disclosed HIV serodiscordant couple, ≥18 years, and not using PrEP or ART at enrollment. Pregnancy testing was conducted when clinically indicated, and HIV-uninfected pregnant women were counseled about the risks and benefits of PrEP use during pregnancy and made a choice about its continuation or discontinuation. Women who continued PrEP attended monthly clinic visits through the duration of their pregnancy and discontinued PrEP after delivery.

Recruitment

All Kenyan HIV-uninfected women enrolled in the Partners Demonstration Project who became pregnant while using PrEP and were offered the opportunity to continue PrEP through their pregnancy were purposively recruited for the qualitative sub-study. Overall, 30 women in the Partners Demonstration Project elected to use PrEP during pregnancy. Of those, 21 women were from study sites in Kenya and were invited to participate in interviews.

The parent study and this qualitative sub-study received approval from the Kenya Medical Research Institute and the University of Washington ethics review boards. All participants provided written informed consent.

Data collection

Semi-structured interview guides were developed collaboratively between study team members (KBS, SBT, MK, KN, GJS, KN, GK) based on literature reviews and experiences in HIV prevention research. These were piloted and translated into Kiswahili and DhoLuo. Interview guides addressed issues specific to the clinical implementation of PrEP during pregnancy and breastfeeding in low-resource settings. Interviews were conducted by trained interviewers in Kiswahili, DhoLuo, or English based in interviewee preference, and later translated to English when necessary. Interviews lasted an average of 36 minutes.

Data analysis

We performed a descriptive analysis using a modified version of the constant comparison method[91] to produce a description of key concepts and themes arising within and between the individual primary categories represented in the interview guides. An initial codebook was developed both deductively from the interview guide and inductively from the transcripts by KBS, SBT, KN, GK, and JP. The codebook was iteratively refined through preliminary coding applications and group discussions. Transcripts were imported into ATLAS.ti v.7 (Scientific Software Development GmbH, Berlin, Germany) for data management and analysis. All

transcripts were coded independently by one member of the study team (GKT, JP, KBS) using the final version of the codebook and their applied codes were reviewed by another member (GKT, JP, KBS). Disagreements in code application were resolved through discussion until consensus was reached. After all data were coded, investigators used an iterative process of reading transcripts, comparing and contrasting coding, and identifying convergent and divergent themes within and between transcripts.

Results

Twenty-one HIV-uninfected women who became pregnant while using PrEP participated in the study (**Table 4**). Almost all women were married (86%) and the mean age was 27 (range 20-36) years; 29% were having their first pregnancy. Three major themes emerged from the interviews related to PrEP use during pregnancy: (1) motivation for PrEP initiation and use during pregnancy, (2) the role of medication side effects and safety concerns on PrEP use, and (3) adherence challenges and successes.

Desire to remain HIV-free and have an HIV-free infant motivated PrEP continuation during pregnancy

Most participants initiated PrEP in order to remain HIV-uninfected. Women described initiating PrEP, when faced with HIV-serodiscordance, as a way of ensuring the stability of their relationship and affirming their love and support for the HIV-infected partner. Having PrEP as an option gave the HIV-infected partner time to accept his HIV status and initiate ART while providing protection from transmission for the woman, allowing her to feel secure in the decision to stay in the relationship. Willingness to initiate PrEP was viewed as a way to demonstrate encouragement for HIV-infected partners to begin ART.

"*The most important thing that made me to join [the Partners Demonstration Project] was because this guy tested positive and I didn't want to leave him in a state where he could lose his life. He would have decided not to use [ART] because he was a very difficult person…he would have just continued drinking [alcohol] the way he was drinking...When I decided [to start PrEP] he saw there is someone who cares. He said, 'Let me just join too' [by taking ART]" (21-year-old woman)*

Women reported that initiating PrEP was the impetus for fulfilling pregnancy desires within HIV-serodiscordant partnerships without fear or worry of HIV transmission. Prior to learning about PrEP, women relied on condoms for HIV prevention and believed they would be unable to have children with their HIV-infected male partners, which was viewed as a threat to their relationship viability.

Initiating PrEP for HIV-uninfected partners and ART for HIV-infected partners prior to pregnancy was seen by women as a collaborative process because both partners worked together to ensure protection against HIV for the infant. Women described attempting pregnancy only post-PrEP and ART initiation because they felt adequately protected from HIV transmission at that time.

"We thought that once I get on the Truvada that [becoming pregnant] should be our first objective because we were seeing that was the only way we were going to sustain the marriage, because you know men, they always want kids. So I decided…we decided actually, the two of us... that we take the Truvada and once we are at good [protection] levels, we could have our baby." (22-year-old woman)

Once pregnant, the primary concern for most participants shifted from personal prevention to preventing HIV for their unborn child. Most women expressed that the desire for their infants to

remain HIV-free was a stronger motivation to continue PrEP during pregnancy than preventing HIV for themselves. Even when condoms were regularly used for HIV prevention, PrEP was seen as an important back-up strategy to ensure infants would be born HIV-uninfected.

> *"I did not want to give birth to a child who has HIV…When you are pregnant and in your own house with your husband, you must make love. And even though we used condoms, sometimes they just don't put it on properly and at times, it just gets out during sexual intercourse. That was also another reason that motivated me to continue using Truvada [during pregnancy], that in case of anything, Truvada was going to help me during the pregnancy." (26-year-old woman)*

Women also felt that continuing PrEP during pregnancy supported their HIV-infected male partners in ART adherence in the longer term. This took different forms, from creating a feeling of being in this together to more tangible support that included taking medications at the same time.

> "*I was taking [PrEP] to motivate my husband to take ART. We set our medication time to be the same so we take medicine together. I would take PrEP and he also takes ART and he would see that we are taking the drugs together." (24-year-old woman)*

The experience of taking PrEP during pregnancy and remaining HIV-uninfected instilled a strong belief that PrEP was effective in preventing HIV. If given the opportunity, women in this study would use PrEP again during pregnancy.

> "*I have used [PrEP] and I haven't sero-converted as they maybe thought someone [in an HIV-serodiscordant couple] could.....I would use it again and again because I think it is effective…*" *(22-year-old woman)*

Having an HIV-free infant outweighed concerns over PrEP side effects and safety

Few women reported any experience of side effects related to PrEP use, and almost all accounts of side effects were limited to early stages of PrEP initiation. Women expressed that the lack of adverse side effects during pregnancy affirmed their belief that PrEP was safe for their unborn infant and that PrEP was helping them.

> "*I have not experienced any side effect so I cannot speak about its [PrEP's] disadvantages. I can only talk about the benefits because I have used it and know how good it is. I have only experienced the beauty of it.*" *(27-year-old woman)*

Dizziness, nausea, vomiting, headaches, and feeling tired were common among women who reported experiencing any side effects while using PrEP during pregnancy. Some women recognized the similarity between pregnancy symptoms and side effects of PrEP and believed one may exaggerate the other. This was seen as a potential barrier to continuing PrEP through pregnancy.

> "*Now if I am pregnant and I am taking [PrEP], it could exaggerate my pregnancy symptoms. If it worsens the symptoms [of pregnancy] like nausea and the drug also has nausea as a side effect, it's a challenge. It [could] make someone to stop the dose.*" *(22-year-old woman)*

Discerning pregnancy symptoms from PrEP side effects caused confusion and distress in some women as they feared their symptoms could be signs of potential danger to their infant from PrEP use. Unilaterally, women respected healthcare providers as knowledgeable and trustworthy conduits of information about PrEP and its side effects. Women found that discussing PrEP use with providers helped them to feel safe and confident with their choice to continue PrEP during pregnancy.

> "*The most important thing was their [health providers'] thoughts. When I got*

pregnant, I had a sign and I was actually shocked. I called the clinic. My legs were swelling and itchy. I called immediately to inform them and inquire whether it was an undesirable side effect [of PrEP]. They asked me to come [to the clinic]. They told me that the most likely cause was the pregnancy because when I started taking Truvada, I did not experience any side effects. My legs started swelling when I got pregnant. But it healed on its own. So they just encouraged me to continue using the drug and true to their word, it did not affect me." *(27-year-old woman)*

Among the few women who experienced side effects from PrEP, some struggled with balancing whether the benefit of using PrEP during pregnancy was worth tolerating side effects. This concern was strengthened by the perception that using PrEP was not necessary for personal treatment and was only for prevention. However, even when symptoms were severe, most women felt the benefit of having a healthy, HIV-free infant outweighed PrEP side effects.

"*These drugs [PrEP] made me sick. I kept thinking that I have no [HIV] virus and these drugs are making me sick. I was asking myself whether I was going to really be fine. I was asking myself every single day, 'Why I am on medication yet I am not sick?' I concluded that the day that I will see my child physically is the day that I will be convinced.*" *(32-year-old woman)*

Women also worried that fetal exposure to PrEP could lead to pregnancy loss or harm their newborn. Some women felt that PrEP use may be less safe during breastfeeding while the infant is growing and eating what the mother eats via breastmilk. However, most women expressed equal concern about the safety of PrEP use during pregnancy and breastfeeding.

"The pregnant woman carries a baby in her womb. What she eats is the same thing that her child will eat. Likewise with the breastfeeding mother…You have to

ask yourself, maybe this baby of mine that is still in the womb can get miscarried or die [because of taking PrEP]. Also with the woman who is breastfeeding. Maybe this child she is carrying, if she eats the drug it can affect the baby, so they will have thoughts or concerns [about using PrEP]" (20-year-old woman)

In all cases, women reported that their own experience of having a healthy infant after using PrEP absolved their safety concerns.

"I didn't see any side effects on my baby and he is still ok. That is what made me to know that there is no way it [PrEP] will affect me health-wise." (21-year-old woman)

Health providers have a positive influence on adherence to PrEP

Some women found remembering to take PrEP daily to be a challenge while others expressed that adherence was not difficult for them. Almost all women recognized that women in HIV-serodiscordant couples would be highly motivated to adhere to PrEP. However, women anticipated adherence would be a challenge if PrEP were offered to all pregnant and breastfeeding women who may not be aware of their HIV risk.

Women viewed healthcare providers as having an important role in facilitating adherence. Continuity between the healthcare providers who counselled women on PrEP pre- and throughout pregnancy supported continuation of PrEP adherence for some women. Health providers who valued the sensitivity of the information being discussed and maintained confidentiality helped cultivate non-judgmental, trusting relationships with women. Positive, well-established supportive relationships with healthcare providers facilitated PrEP adherence throughout pregnancy and beyond.

"*Initially I was coming [for clinic visits] every 3 months but after I got pregnant, [the study staff] changed it to every one month. They are the ones who were attending my pregnancy clinic visits. They would give me and all the care required when someone is pregnant, so it encouraged me to continue [PrEP].*" *(20-year-old woman)*

Discussion

This qualitative study improves understanding of motivations for PrEP use during pregnancy for women in HIV-serodiscordant couples and highlights important concerns and potential barriers for effective PrEP use in this unique population. The main motivator to initiate PrEP pre-pregnancy was remaining HIV-uninfected while the primary motivation to continue PrEP during pregnancy was the desire to have an infant who was HIV-free. Despite being experienced with PrEP prior to pregnancy, participants described uncertainties and confusion in discerning normal pregnancy symptoms from side effects of PrEP. Healthcare providers served as a critical support system for women while using PrEP. As programs consider wider implementation of PrEP to pregnant women at risk for HIV, there is an opportunity to use personal experiences from women who have already used PrEP during pregnancy to improve messaging for pregnant women in the future. Results from this study demonstrate the importance of developing messages that appropriately emphasize the benefits of HIV prevention for mothers and infants while simultaneously acknowledging and addressing concerns of side effects and safety.

Integration of PrEP counseling into routine antenatal care provides an opportunity to introduce PrEP as a female-controlled HIV prevention strategy, especially to women who may be unaware of their male partner's HIV status or unable to negotiate safe sex. Our participants underscored the important role of healthcare providers in addressing concerns and supporting adherence. Discussion of PrEP with healthcare providers early and frequently in antenatal care may help address concerns about side effects and safety within a supportive patient-provider relationship.

Provider-initiated PrEP counseling for pregnant women may also provide an important entry point for addressing other issues in this population, such as male involvement in antenatal care and male partner HIV testing [92, 93].

Some common symptoms of the first trimester of pregnancy overlap with potential side effects of PrEP initiation, including nausea, fatigue, dizziness, and gastrointestinal alterations. In our study, the experience of side effects was a barrier to PrEP continuation and adherence during pregnancy. Women in a first pregnancy have no prior experience with pregnancy symptoms, making it challenging to distinguish between PrEP and pregnancy symptoms. Women who initiate PrEP early in pregnancy may be more likely to confuse pregnancy symptoms with side effects related to PrEP. PrEP initiation prior to becoming pregnant, as was the case with our population, would reduce some of these concerns. Future studies among women who initiate PrEP during pregnancy should evaluate whether side effects and gestational age at PrEP initiation influences patterns of PrEP usage.

There is some evidence that women are more motivated to address health issues during pregnancy to protect their infants [94] and may find it easier to adhere to strategies, like PrEP, during this period. Several studies among HIV-infected women have found that adherence to ART for HIV treatment wanes after perceived risk of MTCT decreases postpartum [95-97]. A similar waning of adherence may occur for PrEP, however there are no data regarding this to date. In our study, women were highly motivated to continue PrEP during pregnancy to ensure their infant would be HIV-free. Adherence to PrEP may be reduced postpartum if perception of the infant's risk of HIV is also reduced. Longitudinal adherence data from women who initiate PrEP in pregnancy through postpartum could inform development of effective messaging to support PrEP adherence beyond pregnancy.

Our study has limitations. Interviews with women who used PrEP during pregnancy were conducted after delivery. Women's concerns about the safety of using PrEP during pregnancy could be influenced by positive recall bias. Future studies should evaluate safety concerns during pregnancy when the birth outcomes are unknown. All participants were in mutually disclosed HIV-serodiscordant couples and expressed strong motivation for preventing HIV. Up to 80% of pregnant African women are unaware of their partner's HIV status and therefore our data cannot be generalized to all pregnant women at risk for HIV [55-57]. Future work should include pregnant women who do not know their male partner's HIV status and who may be less motivated to use PrEP or less able to navigate discreet use of PrEP.

Conclusion

PrEP holds tremendous promise as a female-controlled prevention strategy for pregnant women at high risk of HIV infection, during a time when HIV prevention has dual benefits for mothers and infants. In our study, HIV-uninfected women in HIV-serodiscordant couples were motivated to use PrEP during pregnancy, but had concerns unique to the period of pregnancy. Healthcare providers will be important for PrEP messaging and supporting women on PrEP as programmatic delivery scales up.

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Contributions:

JP and KBS wrote the manuscript. GJS and JMB were the principal investigators of this study and parent study, respectively, and oversaw manuscript preparation. GJS and MK conceived of and designed the substudy. KBS, MK and SBT designed the interview guides. GKT, KBS, KN, and SBT conducted interviews. GKT, JP, KBS, KN and SBT analyzed the data. All authors reviewed and provided comments on the results and final manuscript.

Table 4. Demographic characteristics of participants at enrollment into the parent study

	N (%) or mean (range) n=21
Age, years	27 (20-36)
Currently married	18 (86%)
Number of living children	1 (0-6)
Completed education, years	9 (2-16)
Electricity in the home	16 (76%)
Running water in the home	2 (10%)
Number of people in household	3 (2-6)
Number of rooms in house	2 (1-7)

CHAPTER 5: Maternal tenofovir disoproxil fumarate use during pregnancy is not associated with adverse perinatal outcomes among HIV-infected East African women: a prospective study

Citation: Jillian Pintye, Jared M Baeten, Connie Celum, Nelly Mugo, Kenneth Ngure, Edwin Were, Elizabeth Bukusi, Grace John-Stewart, Renee A Heffron. Maternal tenofovir disoproxil fumarate use during pregnancy is not associated with adverse perinatal outcomes among HIV-infected East African women: a prospective study. AIDS (Submitted April 2017)

Title: Maternal tenofovir disoproxil fumarate use during pregnancy is not associated with adverse perinatal outcomes among HIV-infected East African women: a prospective study

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Abstract

Objectives

Tenofovir disoproxil fumarate (TDF) is commonly used in antiretroviral treatment (ART) and pre-exposure prophylaxis regimens. We evaluated the relationship between adverse perinatal outcomes and prenatal TDF use among HIV-infected women who used 3-drug ART during pregnancy.

Design

Longitudinal data were analyzed from HIV-infected women who became pregnant during two HIV prevention studies (the Partners PrEP Study and the Partners Demonstration Project), conducted among HIV-serodiscordant couples in Kenya and Uganda.

Methods

Pregnancies were included if singleton, not terminated by an induced abortion, had documentation of 3-drug ART use and pregnancy outcome data. Multivariate generalized estimating equation models were used to determine the association of prenatal TDF use and perinatal outcomes.

Results

The median age of pregnant women was 25.4 years and 21% of the 422 included pregnancies were primigravidas. The most frequent ART regimens were TDF/3TC/EFV (39%) and AZT/3TC/NVP (34%); 49% of pregnancies had prenatal TDF exposure and 3% used a protease inhibitor. Neonatal death, preterm birth, and pregnancy loss occurred in 2%, 8% and 12% of pregnancies, respectively. No differences were observed between pregnancies with and without exposure to TDF in the frequency of pregnancy loss (14% vs 9%, adjusted prevalence rate ratio

[aPRR] 1.19, p=0.8), neonatal death (1% vs 2%, aPRR 0.28, p=0.3) or preterm birth (6% vs 10%, aPRR, 0.59, p=0.4).

Conclusions

Maternal TDF use did not adversely affect perinatal outcomes, supporting the safety of maternal TDF use during pregnancy.

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Key words

Africa; ART; obstetrics/gynecology; pregnancy loss; PrEP; prevention of mother-to-child transmission/vertical transmission; tenofovir; preterm birth; women

Introduction

Tenofovir disoproxil fumarate (TDF)-containing combination antiretroviral therapy (ART) is currently a first-line regimen for HIV treatment and Option B+ prevention of mother-to-child transmission (PMTCT) programs encouraged by the World Health Organization (WHO). [19] TDF and the fixed-dose combination of emtricitabine (FTC)/TDF are also recommended by WHO for antiretroviral pre-exposure prophylaxis (PrEP) to prevent HIV acquisition in populations with substantial HIV risk (>3% incidence), which includes pregnant and breastfeeding women in settings where HIV prevalence is high. [98] Although WHO guidelines support PrEP use in pregnancy, national guideline committees have differed in their conclusions regarding PrEP use during pregnancy. For example PrEP use during pregnancy is supported by the Kenyan antiretroviral guidelines but the lack complete of safety data led PrEP to be contraindicated for pregnant women in the current South African PrEP guidelines. [32, 99, 100] To date, most safety data on prenatal TDF use derives from HIV-infected women who used TDF-based ART for HIV treatment with sparse data from HIV-uninfected women who used TDF-containing drugs for PrEP or treatment of hepatitis B virus (HBV). While safety data on prenatal TDF use among HIV-uninfected women accumulate, additional data comparing perinatal outcomes between HIV-infected women who used TDF-based and non-TDF-based ART during pregnancy may contribute to the growing safety profile of prolonged maternal prenatal TDF use.

A recent systematic review [40] that included 33 articles found no statistically significant differences between TDF use during pregnancy and comparison groups in stillbirth/pregnancy loss, preterm delivery, low birth weight, small for gestational age, birth defects, infant or maternal mortality. [101] However, the review included few prospective studies evaluating the relationship of TDF use in pregnancy and perinatal outcomes among African cohorts, and these have mixed results. [88, 102-104] Recently, the PROMISE (Promoting Maternal-Infant Survival Everywhere) study found higher rates of adverse perinatal outcomes (low birth weight, very

preterm birth, and early infant death) among HIV-infected African mothers using TDF-based ART compared to zidovudine (AZT)-based ART, however, this was in the context of protease-inhibitor-based regimens which may have been an effect modifier. [102] Other studies have not found similar associations between TDF-based vs. non-TDF-based PMTCT regimens in African cohorts. [104]

We evaluated whether pregnancy loss, preterm birth and neonatal death were more frequent in a cohort of Kenyan and Ugandan HIV-infected women who used TDF-containing ART during pregnancy compared to HIV-infected women who used ART during pregnancy that did not contain TDF.

Methods

Study population and procedures

Longitudinal data were analyzed from women who were HIV-infected at enrollment and became pregnant during two studies (the Partners PrEP Study and the Partners Demonstration Project). The Partners PrEP Study was a randomized clinical trial of the safety and efficacy of daily oral PrEP for the prevention of HIV acquisition; 4758 HIV-serodiscordant couples from 9 sites in Kenya and Uganda were enrolled and followed between 2008 and 2012. [15] The Partners Demonstration Project was an open-label implementation project evaluating the integrated delivery of PrEP and ART for HIV prevention that enrolled and followed 1013 high risk HIV-serodiscordant couples at 4 sites in Kenya and Uganda between 2012 and 2016. [90] At enrollment into both studies, all participants were members of a mutually-disclosed HIV-serodiscordant couple, ≥18 years, and not using PrEP or ART. [90, 105]

In both studies, HIV-infected partners were followed quarterly and monitored 6-monthly for CD4 counts, WHO clinical staging, and HIV RNA levels. HIV-infected participants were referred to local clinics of their choice, including those co-located with the research clinic, to initiate

treatment once eligible according to national guidelines.[15, 90] In both studies, pregnancy testing for HIV-infected women was performed when clinically indicated and women attended quarterly study visits through the duration of their pregnancy.

Definition of exposures and outcomes

The primary exposure was the use of any TDF-containing 3-drug ART during pregnancy. TDF use was captured as part of information on maternal ART use during pregnancy, including the type of ART regimen and date of initiation self-reported by women and verified with clinical records or pill bottles when available. ART use during pregnancy was categorized as having been initiated before pregnancy, during the first trimester, or after the first trimester. Sociodemographic characteristics and obstetrical history were also collected through self-report.

Our three primary outcomes were pregnancy loss (any, <20 weeks and ≥20 weeks), neonatal death within three days of delivery following live birth and preterm birth (live birth <37 weeks gestation). Last menstrual period (LMP), pregnancy outcome (induced abortion, pregnancy loss or live birth), the date the pregnancy ended and occurrence of neonatal death were self-reported by women. Gestational age at birth or pregnancy loss was calculated by subtracting date of pregnancy end from LMP.

Statistical analysis

Pregnancies were included in the primary analysis if they were singleton, did not terminate by induced abortion, had documentation of 3-drug ART regimen used during pregnancy and had pregnancy outcome data available. Fisher's exact tests for proportions and Kruskal-Wallis tests for continuous measures were used to detect differences in sociodemographic and clinical characteristics between women exposed and unexposed to TDF during pregnancy. All analyses of pregnancy loss were restricted to women who initiated 3-drug ART before pregnancy or during the first trimester to ensure ART exposure preceded pregnancy loss.

Generalized estimating equation (GEE) log-binomial regression models were used to determine the association of TDF-containing 3-drug ART use during pregnancy and pregnancy loss, neonatal death, and preterm birth with use of non-TDF 3-drug ART use as the reference group. We decided *a priori* to adjust multivariate GEE models for study cohort and maternal age. Additionally, we assessed maternal education, number of children, marital status, time since HIV diagnosis, time since ART initiation, CD4+ lymphocyte count (cells/μl), maternal viral load (plasma HIV RNA [$\log_{10}$ copies/ml]), WHO clinical stage, and protease inhibitor use as potential covariates. We included covariates in the final model that changed the measure of association by >10% (crude vs adjusted). For variables that were collinear (time since ART initiation, CD4+ lymphocyte count, HIV RNA viral load, and WHO clinical stage), we included the variable with the least amount of missing data in multivariate models.

Sensitivity analyses

We also compared the frequency of adverse perinatal outcomes between pregnancies with exposure to 3-drug ART combinations containing TDF versus AZT. Pregnancies were included in the sub-analyses if the mothers prenatally used ART that did not contain protease-inhibitors but contained either TDF or AZT, but not both. To address missing data, we performed additional sensitivity analyses by repeating our primary analyses including pregnancies that were missing birth outcome data but met all other inclusion criteria by: 1) assuming all pregnancies with missing outcome data had each respective adverse perinatal outcome, 2) assuming all pregnancies with missing outcome data did not have each respective adverse perinatal outcome, and 3) using multiple imputation to predict each respective perinatal outcome among pregnancies missing outcome data. [106]

Results

Demographics and TDF exposure

In total, 422 pregnancies (25% of the total pregnancies to HIV-infected women in the cohorts) met inclusion criteria and were included in the primary analysis (**Figure 7**). The median age of pregnant women was 25.4 years (interquartile range [IQR] 20.5-29.9), 21% were primigravidas, and over half of women (57%) were WHO Stage I at their first pregnancy visit. Overall, the most frequently used ART regimens were TDF/3TC/EFV (39%) and AZT/3TC/NVP (34%). Among the 208 (49%) pregnancies with prenatal TDF exposure, the most frequently used ART regimens were TDF/3TC/EFV (n=167, 80%) and TDF/3TC/NVP (n=31, 15%). Among pregnancies without TDF exposure (n=214, 51% of all pregnancies), AZT/3TC/NVP (n=146, 68%); AZT/3TC/EFV (n=20, 9%), AZT/3TC/LPV/r (n=19, 9%) and d4T/3TC/NVP (n=19, 9%) were the ART regimens most frequently used during pregnancy. Overall, the frequency of protease-inhibitor use was low (3%). Compared to women who used non-TDF containing ART during pregnancy, women who used TDF-containing ART were younger, more educated, had fewer children, more frequently initiated ART before pregnancy or during the first trimester, had lower viral loads and used regimens that contained protease-inhibitors less frequently (**Table 5**).

Perinatal outcomes

Among pregnancies in which 3-drug ART was initiated before pregnancy or during the first trimester (n=204), pregnancy loss occurred in 24 (12%) pregnancies; 79% of these losses occurred at <20 weeks gestation. Neonatal death and preterm birth occurred in 2% and 8% of pregnancies with live births (n=380), respectively (**Table 6**).

Among pregnancies with exposure to 3-drug ART in the first trimester, there was no difference in the frequency of any pregnancy loss between those with TDF-containing ART exposure compared to regimens without TDF (14% versus 9%, respectively, prevalence ratio [PRR]=1.63, 95% CI 0.66-4.04, p=0.2). There was also no difference between exposure groups in the

subgroup of losses <20 weeks gestation (11% vs 7%, PRR=1.49, 95% CI 0.54-4.12, p=0.4) nor in the subgroup of pregnancy losses ≥20 weeks gestation (2% vs 1%, PRR=2.79, 95% CI 0.32-24.63, p=0.4). Among pregnancies that resulted in live births, there were no differences between pregnancies with prenatal TDF-containing ART use compared to non-TDF-containing ART use in the frequency of neonatal death (1% versus 2%, PRR=0.82, 95% CI 0.19-3.57, p=0.8) or preterm birth (6% versus 10%, PRR=0.55, 95% CI 0.27-1.14, p=0.1). In multivariate models, we did not detect any association between prenatal TDF use and any adverse perinatal outcome after adjustment for study cohort, maternal age, time since maternal HIV diagnosis, and WHO stage at first pregnancy visit (**Table 7, Model 1**).

Sensitivity analyses

In total, 371 pregnancies had exposure to either TDF- or AZT-containing 3-drug ART, did not contain both TDF and AZT, and did not contain protease-inhibitors. Among those 371 pregnancies, 169 (46%) had TDF exposure and 202 (54%) had AZT exposure; 184/371 (50%) had first trimester ART exposure. There was no difference in the frequency of loss at <20 weeks between pregnancies with first trimester exposure to TDF- vs AZT-containing 3-drug ART (11% vs 8%, respectively, p=0.6); no losses ≥20 weeks occurred among pregnancies with first trimester exposure to AZT-containing ART and 4 occurred among those with exposure to TDF-containing ART (p=0.3). Among pregnancies with live births, we did not detect differences between exposure to TDF- or AZT-containing ART in the frequency of neonatal death (2% vs 2%, p=0.9) or preterm birth (6% vs 10%, p=0.2).

In addition to the 422 included in the primary analysis, 29 pregnancies were missing perinatal outcome data but met all other inclusion criteria; 24/29 (83%) of these pregnancies had exposure to prenatal TDF use. Results from separate multivariate GEE models that included all

451 pregnancies and accounted for missing outcomes data by assuming all 29 pregnancies did or did not have each respective adverse perinatal outcome and multiple imputation models were similar to our primary results (Table 3, Models 2-4).

Discussion

In this prospective analysis of pregnancies among HIV-infected Kenyan and Ugandan women who used 3-drug ART during pregnancy, exposure to prenatal TDF use was not associated with adverse perinatal outcomes. Compared to pregnancies with first trimester exposure to 3-drug ART regimens that did not contain TDF, we found no difference in the frequency of pregnancy loss among pregnancies with TDF exposure in the first trimester. In addition, we found no association between exposure to prenatal TDF use and neonatal death or preterm birth. Our findings support the growing evidence that prenatal TDF use is not associated with adverse perinatal outcomes and contribute to the few prospective studies evaluating the safety of TDF use during pregnancy from African cohorts.

Our finding that TDF-containing ART use during the first trimester was not associated with pregnancy loss <20 weeks compared to non-TDF-containing ART use is novel as previous analyses have not reported on the association prenatal TDF use and pregnancy loss at earlier than 20 weeks (excluding induced abortions) among HIV-infected women. The multi-country Development of AntiRetroviral Therapy in Africa (DART) trial found no difference in the frequency of pregnancy losses <22 weeks between HIV-infected women not on TDF-containing ART versus those on TDF-containing ART, though spontaneous and induced abortions were combined (62/137 pregnancies ending <22 weeks were induced abortions in DART). [88] Two analyses which used data from HIV-uninfected African women enrolled in PrEP efficacy clinical trials who became pregnant while on PrEP and had in utero PrEP exposure for approximately 5

weeks found that risk of early pregnancy loss was not higher among women exposed to TDF-containing PrEP compared to placebo. [26, 107]

Most pregnant women in sub-Saharan African settings present for their first antenatal care (ANC) visit during the second or third trimester, [108, 109] and therefore ART safety studies that enroll women from ANC or abstract ANC records likely miss early pregnancy losses. Among pregnancy losses that were not induced, the frequency of pregnancy losses occurring >20 weeks (21%) in our study may be higher than observed in settings without regular pregnancy testing, though it is similar to other studies among HIV-infected African women such as the DART trial in which 26% of non-induced pregnancy losses occurred at >22 weeks. [88] Future safety studies that enroll women prior to or early in pregnancy and evaluate longer in utero TDF exposure could be helpful for assessing the association of TDF use and early pregnancy loss and other adverse neonatal outcomes. Similar to other studies among African cohorts that compared stillbirth in HIV-infected women receiving TDF- or non-TDF ART [88, 103, 104], we found no differences in pregnancy loss at ≥20 weeks between pregnancies with and without TDF exposure.

Our finding that prenatal TDF-containing ART use among HIV-infected mothers was not associated with preterm birth or neonatal death compared to non-TDF-containing ART is similar to other prospective studies in African cohorts. [88, 103, 104] In the PROMISE study, TDF-based ART was associated with higher rates of very preterm birth <34 weeks gestation (6.0% vs. 2.6%, p=0.04) and infant death within the first 14 days of life (4.4% vs. 0.6%, P=0.001), relative to AZT-based ART. [102] Data have suggested a possible pharmacokinetic interaction between lopinavir-ritonavir and TDF which may explain the PROMISE results. [110, 111] In contrast to the PROMISE study, our study had infrequent protease-inhibitor use among TDF-users (33% vs 3%) [110, 111] When we excluded women who used a protease-inhibitor containing ART regimen, we did not detect differences in the frequency of preterm birth or

neonatal death between pregnancies that had exposure to either TDF- or AZT-containing 3-drug ART.

Our relatively small sample size may have limited our power to detect statistical differences, though our sample size is comparable to previous studies examining the relationship of between prenatal TDF use and perinatal outcomes. We also adjusted for characteristics that differed between TDF-users and non-users that may have further decreased our statistical power in multivariate models. Larger population-based surveillance studies in African settings with adequate power to detect differences in rare outcomes like neonatal death will be important as TDF-based regimens continue to be rolled out for HIV treatment and prevention. Information on birth weight, birth length and infant growth outcomes were not captured for HIV-infected mothers enrolled in the Partners PrEP Study or the Partners Demonstration Project. Few studies have assessed the effects of prolonged prenatal TDF use on postnatal infant growth and bone health [86, 87, 89, 112, 113], with only two in African populations [85, 88], and these have mixed results. Additional longitudinal studies that evaluate longer-term postnatal outcomes of TDF use during pregnancy, including infant and child cognitive growth, are needed.

Our findings are reassuring and complement the growing body of literature indicating that TDF use during pregnancy is not associated with adverse perinatal outcomes compared to non-TDF-containing ART regimens. More specifically, our study contributes to the very limited data available on safety of TDF use during early pregnancy and did not find an association with first trimester TDF exposure and pregnancy loss at <20 weeks. Further research on longer-term effects of maternal prenatal TDF use is important given the majority of HIV-infected women are prescribed a TDF-containing PMTCT regimen. In addition, data on the safety of TDF as PrEP are needed from HIV-negative pregnant women, given PrEP scale-up in settings where fertility and HIV acquisition rates in pregnant women are high.

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Figure 7. Flowchart of inclusion

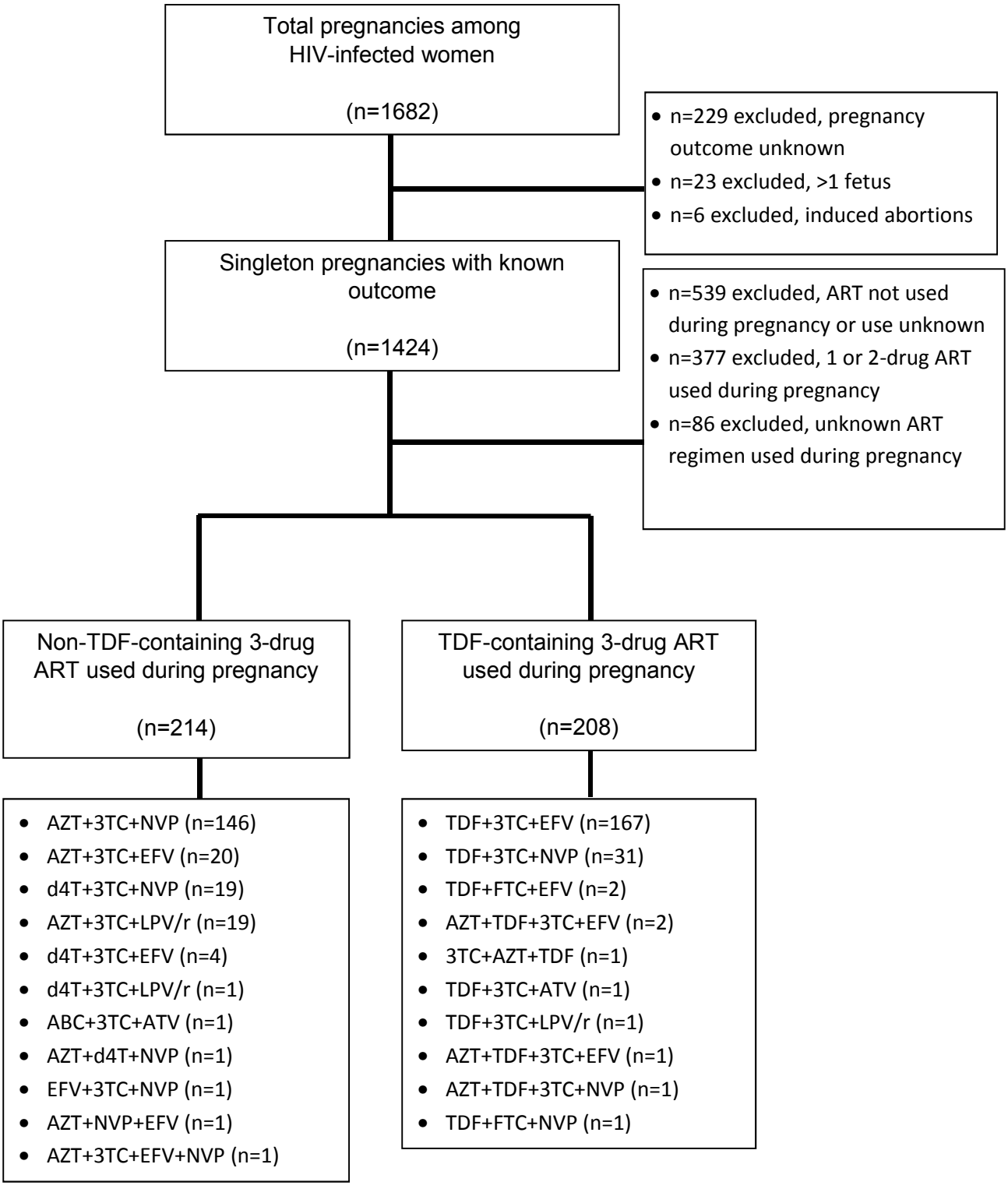

Table 5. Demographic and clinical characteristics by prenatal TDF use among HIV-infected women that used 3-drug ART during pregnancy

Characteristic	N (%) or Median (IQR)[1]		p-value[4]
	All HIV-infected women[2]		
	No TDF use (n=214)	Any TDF use[3] (n=208)	
Demographic			
Age (years)	26.6 (23.5-31.6)	24.7 (21.7-28.5)	**0.001***
Education completed (years)	7 (5-9)	8 (7-11)	**0.010***
Number of children	2 (1-3)	1 (0-2)	**<0.001***
Married	201 (98.1%)	187 (96.4%)	0.312
Clinical			
Time since first HIV diagnosis (years)	0.4 (0.1-2.0)	0.2 (0.1-1.2)	**0.055***
Timing of ART initiation			
Before pregnancy	55 (26.4%)	80 (39.2%)	**<0.001***
First trimester	27 (13.0%)	42 (20.6%)	
Second or third trimester	126 (60.6%)	82 (40.2%)	
CD4 (cell/μl)	526 (394-753)	739 (504-912)	
Plasma HIV RNA (log_{10} copies/ml)	5.5 (3.7-8.8)	3.7 (3.0-4.0)	**<0.001***
WHO clinical stage			
Stage 1	97 (50%)	120 (64%)	**0.002**
Stage 2	71 (37%)	61 (32%)	
Stage 3	24 (12%)	7 (4%)	
Stage 4	2 (1%)	0 (0%)	
PI-containing maternal ART regimen	11 (5%)	3 (1%)	**0.015***

*p<0.10; TDF=tenofovir disoproxil fumarate; PI=protease-inhibitor

[1] Missing data not shown
[2] Among HIV-infected women with documented use of any 3-drug ART during pregnancy
[3] Maternal TDF use defined as documented use of TDF-containing 3-drug ART during pregnancy
[4] Chi-squared test for proportions or Kruskal-Wallis test for continuous measures; Fisher's exact test for variables with ≤5 observations

Table 6. Distribution of adverse pregnancy outcomes among HIV-infected women who used 3-drug ART during pregnancy, by regimen

	N (%)									
	TDF-containing 3-drug ART				Non-TDF-containing 3-drug ART					
		TDF+				AZT+				
Perinatal outcome	Any (n=208)	3TC+EFV (n=167)	3TC+NVP (n=31)	Other[1] (n=10)	Any (n=214)	3TC+NVP (n=146)	3TC+EFV (n=20)	3TC+LPV/r (n=19)	d4T+3TC+NVP (n=19)	Other[2] (n=10)
Pregnancy loss[3]										
Any[3]	17 (14%)	13 (13%)	4 (18%)	0 (0%)	7 (9%)	5 (8%)	0 (0%)	0 (0%)	1 (8%)	1 (20%)
<20 weeks[3]	13 (11%)	9 (10%)	4 (18%)	0 (0%)	6 (7%)	5 (8%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
≥20 weeks[3]	4 (2%)	4 (4%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)
Neonatal death[4]	3 (1%)	3 (2%)	0 (0%)	0 (0%)	4 (2%)	3 (2%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Preterm birth[4,5]	10 (6%)	9 (6%)	1 (4%)	0 (0%)	20 (10%)	14 (10%)	2 (11%)	0 (0%)	2 (12%)	2 (22%)

TDF=tenofovir disoproxil fumarate; 3TC=lamivudine; EFV=efavirenz; NVP=nevirapine; AZT=zidovudine; LPV/r=lopinavir/ritonavir; d4T=stavudine

[1] Other TDF-containing regimens include TDF+FTC+EFV (n=2), AZT+TDF+3TC+EFV (n=2), 3TC+AZT+TDF (n=1), TDF+3TC+atazanavir (n=1), TDF+3TC+LPV/r (n=1), AZT+TDF+3TC+EFV (n=1), AZT+TDF+3TC+NVP (n=1) and TDF+NVP+emtricitabine (n=1)
[2] Other non-TDF-containing regimens include d4T+3TC+EFV (n=4), d4T+3TC+LPV/r (n=1), 3TC+atazanavir+abacavir (n=1), AZT+d4T+NVP (n=1), EFV+3TC+NVP (n=1), AZT+NVP+EFV (n=1) and AZT+3TC+NVP+EFV (n=1)[3] Fisher's exact p-value compares the frequency of pregnancy loss, neonatal death and preterm birth between pregnancies with exposure to any TDF-containing 3-drug ART during pregnancy and pregnancies without any TDF-containing 3-drug ART during pregnancy
[3] Among pregnancies in which 3-drug ART was initiated before pregnancy or during the first trimester (n=204)
[4] Among live births (n=380)
[5] Preterm birth defined as gestational age <37 weeks at birth

Table 7. Association of adverse perinatal outcomes and prenatal TDF use among HIV-infected women who used 3-drug ART during pregnancy[1,2]

	Univariate		Multivariate[3]							
			Model 1[5]		Model 2[6]		Model 3[7]		Model 4[8]	
Perinatal outcome	**PRR (crude) (95% CI)**	**P[4]**	**Adj PRR (95% CI)**	**P[4]**	**Adj PRR[4] (95% CI)**	**P[4]**	**Adj PRR (95% CI)**	**P[4]**	**Adj PRR) (95% CI)**	**P[4]**
Pregnancy loss[9]										
Any	1.63 (0.66-4.04)	0.3	1.19 (0.32-4.49)	0.8	1.08 (0.34-3.29)	0.9	1.20 (0.32-4.54)	0.8	0.54 (0.16-1.82)	0.3
<20 weeks	1.49 (0.54-4.12)	0.4	1.21 (0.48-13.32)	0.8	1.07 (0.30-3.80)	0.9	1.22 (0.23-6.39)	0.8	0.44 (0.10-1.97)	0.3
≥20 weeks	2.79 (0.32-24.63)	0.4	1.17 (0.34-4.06)	0.8	0.95 (0.21-4.38)	0.7	1.18 (0.34-4.08)	0.8	1.32 (0.34-5.10)	0.7
Neonatal death[10]	0.82 (0.19-3.57)	0.8	0.28 (0.02-4.00)	0.3	1.91 (0.83-4.38)	0.1	0.27 (0.02-3.73)	0.3	0.63 (0.10-4.03)	0.6
Preterm birth[10, 11]	0.55 (0.27-1.14)	0.1	0.59 (0.19-1.84)	0.4	1.35 (0.68-2.66)	0.4	0.54 (0.18-1.56)	0.3	0.49 (0.15-1.58)	0.2

*p<0.05; TDF=tenofovir disoproxil fumarate; PRR=Prevalence rate ratio; Adj PRR=adjusted prevalence rate ratio; p=p-value

[1] Pregnancies occurring among HIV-infected women with documented use of any 3-drug ART during pregnancy
[2] Maternal TDF use defined as documented use of TDF-containing 3-drug ART during pregnancy
[3] Multivariate models adjusted for study cohort, maternal age, time since HIV diagnosis and WHO stage at first pregnancy visit
[4] p-value for log-binomial generalized estimating equations (GEE) models
[5] Model 1 is a complete case analysis of 422 pregnancies that met inclusion criteria and had birth outcome information available
[6] Model 2 includes 451 pregnancies that met inclusion criteria and assumes 29 pregnancies with missing outcome information had the respective adverse perinatal outcome
[7] Model 3 includes 451 pregnancies that met inclusion criteria and assumes 29 pregnancies with missing outcome information did not have the respective adverse perinatal outcome
[8] Model 4 includes 451 pregnancies that met inclusion criteria and used multiple imputation to predict the respective adverse perinatal outcomes for 29 pregnancies missing outcome data
[9] Among pregnancies in which 3-drug ART was initiated before pregnancy or during the first trimester
[10] Among live births.
[11] Preterm birth defined as gestational age <37 weeks at birth.

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