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Pregnancy outcomes and infant growth among babies with in utero exposure to tenofovir-based pre-exposure prophylaxis for HIV prevention

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Author contributions

RH and JMB conceived the study. RH wrote the first draft of the manuscript. TH performed statistical analyses. JMB, CC, and RH were awarded grants to fund the study. MM oversaw laboratory technicians that performed analyses of tenofovir concentrations. NM, KN, SA, EK, EB, JO, ET and NB led the site teams that collected the data. All authors contributed critical revisions to the analysis and interpretation and reviewed the final manuscript draft.

Conflicts of Interest

The authors declare no conflicts of interest. Gilead Sciences donated the PrEP medication but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Abstract

Background: Global guidelines recommend pre-exposure prophylaxis (PrEP) use by women at risk for HIV, including during pregnancy, a period with heightened HIV risk. However, data to support safety of PrEP use during pregnancy are limited, particularly from women using PrEP throughout pregnancy.

Methods: In an open-label delivery study of PrEP integrated with ART for high risk HIV serodiscordant couples in Kenya and Uganda (the Partners Demonstration Project), women who became pregnant while using PrEP were offered the option to continue PrEP throughout pregnancy. We compared pregnancy outcomes and one-year infant growth from pregnancies with exposure to PrEP throughout pregnancy to those without any exposure, with data from the placebo arm of a prior efficacy trial of PrEP conducted in the same setting.

Results: Outcomes from 30 women who elected to continue PrEP throughout pregnancy were compared to those from 96 pregnancies among PrEP-unexposed women. There were small non-significant decreases in the frequency of pregnancy loss (16.7% PrEP-exposed versus 23.5% PrEP-unexposed, adjusted odds ratio [aOR]=0.59, p=0.4) and preterm delivery (0 versus 7.7%, [aOR]=0.54, exact p=0.6). No congenital anomalies occurred among PrEP-exposed infants. PrEP-exposed infants had slightly lower adjusted mean z-scores for length (-1.73 versus -0.79, p=0.05) and head circumference (0.24 versus 1.07, p=0.04) one month after birth but were comparable to PrEP-unexposed infants in these measurements one year after birth.

Conclusions: This first evaluation among women using PrEP throughout pregnancy indicates no greater frequency of adverse pregnancy outcomes or restricted infant growth; these findings support recommendations permitting PrEP use during pregnancy.

Keywords

pregnancy; PrEP; HIV prevention; pregnancy outcomes; infant growth

BACKGROUND

Oral pre-exposure prophylaxis (PrEP) using tenofovir-based antiretrovirals, particularly the combination emtricitabine/tenofovir disoproxil fumarate (FTC/TDC), is a recommended HIV prevention strategy for individuals with substantial risk of HIV infection (1–3). Risk of HIV infection is heightened during pregnancy, likely due to behavioral and biologic factors, and interventions to safely protect women against HIV acquisition during pregnancy are a priority (4–6). Global guidelines recommend PrEP for HIV prevention during pregnancy (3, 7); however, only data from women living with HIV using tenofovir as part of combination HIV treatment regimens and women treating Hepatitis B are available to contribute to safety considerations for PrEP when used during pregnancy (8). These prior studies have established a lack of teratogenicity with tenofovir use during pregnancy (9) but some have suggested that *in utero* tenofovir exposure could lead to stunting in infant bone growth (10–12).

In an open-label PrEP demonstration study in Kenya and Uganda, women who became pregnant while using PrEP were offered the choice to continue PrEP throughout their pregnancy. We assessed pregnancy outcomes and infant growth characteristics, and compared PrEP-exposed pregnancies to PrEP-unexposed pregnancies observed among women randomized to the placebo arm of a separate PrEP efficacy trial.

METHODS

Data were from women enrolled in two longitudinal studies of tenofovir-based PrEP. PrEP-exposed women were participating in the Partners Demonstration Project, an open-label PrEP delivery study for high-risk HIV serodiscordant couples in 4 sites in Kenya and Uganda conducted from 2012–2016. Study procedures included quarterly study visits with the provision of PrEP until the point when the partner living with HIV had used ART for at least 6 months. HIV-negative participants had normal kidney function at enrollment (hepatitis B surface antigen negative and creatinine clearance >60 ml/min) and had 6-monthly creatinine monitoring. At each visit, HIV-negative partners were tested for HIV, screened for acute HIV symptoms, dispensed FTC/TDF PrEP, and counseled about adherence to the daily PrEP regimen. Point-of-care urine β -human chorionic gonadotropin (hCG) tests were conducted to identify pregnancy at the study screening visit and as clinically indicated thereafter (e.g., when missed menses was reported).

A mid-study protocol modification allowed women becoming pregnant while on PrEP the opportunity to have monthly visits during pregnancy (for more frequent clinical monitoring), the choice to discontinue PrEP during pregnancy or continue following a monthly dispensing schedule, and to have their infants enrolled for quarterly measurement of length, weight, and head circumference during their first year. Additional counseling at the time of pregnancy discovery focused on the risks and benefits of PrEP use during pregnancy including the largely reassuring data on pregnancy outcomes and infant growth among women using TDF and FTC as part of combination HIV treatment, the risk of incident HIV infection during pregnancy, and consequences of acute maternal HIV infection to babies.

Participants using PrEP were issued electronic medication event monitoring (MEMS) bottle caps that recorded the date and time when every opening occurred. Additionally, archived plasma samples collected monthly from pregnant women dispensed PrEP were shipped on dry ice to the Clinical Pharmacology Analytical Laboratory at Johns Hopkins University for tenofovir quantification using liquid chromatographic-tandem mass spectrometry (LC-MS/MS), with a limit of quantification of 0.31 ng/ml (13).

For comparison, data from PrEP-unexposed pregnancies were contributed by women in the placebo arm of the Partners PrEP Study, a phase III, double-blind PrEP efficacy study conducted at 9 clinical research sites in Kenya and Uganda from 2008–2012. At enrolment, HIV-negative participants had normal kidney function and were not infected with hepatitis B (14). HIV-negative partners completed monthly study visits for HIV testing, study drug dispensing, adherence counseling, and urine hCG testing. Study drug was withheld from women at their first positive pregnancy test result; pregnant women remained in the study and their infants were enrolled for quarterly measurement of length, weight, and head circumference during their first year.

In both studies, obstetric history was collected through self-report and the outcome of the current pregnancy was verified through antenatal records with careful follow up by the study safety monitor to ensure data completeness and accuracy. Any woman who seroconverted to HIV while pregnant was immediately referred for prevention of mother to child services and study staff followed the case to ensure efficient antiretroviral initiation. Infants born to HIV-infected mothers were tested for HIV according to national guidelines, which included DNA polymerase chain reaction testing at 6 weeks after birth; results were recorded on study forms after study staff verified with the infant's clinic records.

Statistical methods

Multiple regression analyses compared pregnancy outcomes and infant growth among pregnancies exposed and unexposed to PrEP. For comparisons of pregnancy loss, multivariable generalized estimating equations were used to account for multiple pregnancies per woman. For comparisons of preterm delivery of a live birth and congenital anomalies, exact logistic regression was used since there were no preterm deliveries or congenital anomalies among babies exposed to PrEP. For comparisons of growth characteristics, the 2006 WHO growth standard by age in days was used to calculate age- and sex- adjusted z-scores for infants born at term (gestational age ≥ 37 weeks) (15); for infants born <37 weeks, preterm growth standards were used and z-scores were adjusted for gestational age (16). Two sample t-tests were used to test the difference between PrEP-exposed and PrEP-unexposed infant growth at each time point and linear mixed-effects models were used to compare the growth trajectories over time. SAS 9.4 (NC, USA) was used for all analyses.

Protection of human subjects

The protocols for both studies were approved by the Human Subjects Division at the University of Washington and local ethics committees for each site. Written informed consent was obtained from all participants in English or their preferred local language.

RESULTS

In the Partners Demonstration Project, 30 pregnancies from 30 women were exposed to PrEP (88% of women offered the choice to continue PrEP during pregnancy). In the Partners PrEP Study, 88 women from the placebo arm with no exposure to PrEP reported 96 pregnancies. PrEP-exposed women were slightly younger than PrEP-unexposed women (median age 25 versus 28), had no children more frequently (46.7% versus 13.6%), and greater likelihood for HIV acquisition from their HIV-infected male partners (risk scores=7 versus 4 based on a validated tool) (17). Maternal obstetric histories were similar including the frequency of prior pregnancy loss (23.3% PrEP-exposed and 39.6% PrEP-unexposed, $p=0.1$), preterm live births (0% PrEP-exposed and 9.4% PrEP-unexposed, $p=0.1$), and other complications (0 in both cohorts). No women from the PrEP-exposed cohort seroconverted to HIV during pregnancy while 6 women unexposed to PrEP seroconverted. No babies were HIV-infected at birth.

Among women offered PrEP during pregnancy, 22 (73.3%) were dispensed PrEP at least once and two elected to discontinue PrEP prior to the end of pregnancy. Women were dispensed PrEP a median of 6 months (IQR 4–8) during pregnancy. Based on MEMS data, 52% of women took 80% of expected doses. Based on plasma tenofovir quantification, 74% (115/154) of samples had tenofovir detected and 40.3% had concentrations $\geq 35\text{ng/mL}$, consistent with daily PrEP use (18).

Of the 30 pregnancies that were PrEP-exposed, 83% resulted in a live birth and 17% resulted in a pregnancy loss (7% at <20 weeks and 10% at 20–36 weeks, Table 1). The frequency of live birth was similar among PrEP-unexposed pregnancies (live birth = 68%, $p=0.10$). There were no preterm deliveries among the 25 live births with PrEP exposure, which was not statistically different from those without PrEP exposure (7.7% of PrEP-unexposed births were preterm, $p=0.4$). There were no congenital anomalies present in babies born to women using PrEP and 5 babies (7.7%) with congenital anomalies born to women with no PrEP exposure ($p=0.6$ for the difference in frequency).

Quarterly infant growth measurements from birth to 1 year were conducted for 93% of all expected visits after accounting for 4 infant deaths in the PrEP-unexposed cohort. Z-scores for infant weight were similar between PrEP-exposed and PrEP-unexposed infants at every quarterly visit (Figure 1a). Adjusted z-scores for length were slightly lower for PrEP-exposed infants at month 1 (mean z-score -1.73 for the PrEP-exposed vs. -0.79 for the PrEP-unexposed, $p=0.05$) and month 3 (mean z-score -1.66 vs. z-score -0.42 , $p=0.02$, Figure 1b). However, by 12 months, length z-scores were higher for PrEP-exposed infants (z-score for the PrEP-exposed -0.03 vs. -1.07 , $p=0.03$). Head circumference followed a similar pattern with a slightly lower head circumference for PrEP-exposed infants at birth (mean z-score 0.24 for the PrEP-exposed vs. 1.07 for the PrEP-unexposed, $p=0.04$) and similar head circumference at 12 months (mean z-score -0.01 vs. 0.3 , $p=0.4$, Figure 1c). In linear mixed-effect regression models, the slope for z-scores for weight and length were statistically greater among PrEP-exposed relative to PrEP-unexposed infants ($p<0.001$ for both of the slope differences) while the slope difference for head circumference was not statistically different ($p=0.07$). Results were similar in separate sensitivity analyses that: 1)

restricted to infants that had complete follow up data for one year after birth (n=17 PrEP-exposed and 49 PrEP-unexposed infants) and 2) included only PrEP-exposed infants whose mothers had tenofovir detected in at least 75% of samples collected during pregnancy (n=11).

DISCUSSION

To our knowledge, these are the first data to assess pregnancy outcomes and infant growth among HIV-negative women who used tenofovir-based PrEP throughout pregnancy to prevent HIV acquisition. The frequency of pregnancy loss, preterm delivery, and congenital anomalies were not different when mothers used PrEP throughout pregnancy. While some of the measures of infant size were smaller at birth for infants exposed to PrEP, PrEP-exposed and unexposed infants were of similar average size one year after birth. Our sample size is small and while these results are reassuring, they should be regarded as preliminary, potentially laying expectations that the findings be upheld in larger cohorts and registry data. In resource-constrained settings, the background prevalence of preterm birth and low birth weight is 12% and 16% (19, 20) while 2.7% of babies born with antiretroviral exposure have congenital anomaly (21). Our data are also reassuring relative to these rates.

Nearly 90% of women elected to continue PrEP during pregnancy. However, our MEMS data, corroborated by TFV quantification, suggest that not all women were fully adherent to the daily dosing regimen. More data are needed to establish therapeutic levels of TFV during pregnancy, as hemodilution may impact tenofovir availability. An immediate priority is to formulate messages for pregnant women using PrEP during pregnancy that describe elevated HIV risk and PrEP adherence information.

In many regions, and especially those where women bear a great burden of HIV infection, women spend a substantial proportion of their reproductive years pregnant and PrEP offers a safe HIV prevention option. As PrEP delivery becomes widespread in these regions, children exposed to PrEP during organogenesis and fetal development and early in infancy can continue to be monitored and contribute more safety data. For women with substantial HIV risk, our data uphold current WHO recommendations about PrEP use during pregnancy.

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Figure 1.

Age and gender-adjusted z-scores for infant a) weight, b) length, and c) head circumference. Slopes for z-scores for weight (0.01 for PrEP-exposed and -0.06 for PrEP-unexposed, slope difference=0.07) and length (0.19 for PrEP-exposed and -0.04 for PrEP-unexposed, slope difference=0.23) are greater among PrEP-exposed relative to PrEP-unexposed infants ($p<0.001$ for both). In sensitivity analysis restricted to infants with complete follow up data for one year, trajectories were similar: for weight, slopes for z-scores are 0.01 for PrEP-exposed and -0.06 for PrEP-unexposed (slope difference=0.07, $p=0.005$); for length, slopes for z-scores are 0.16 for PrEP-exposed and -0.04 for PrEP-unexposed (slope difference=0.2, $p<0.001$). In sensitivity analysis restricted to infants whose mothers had tenofovir detected in at least 75% of samples collected during pregnancy, trajectories were also similar: for weight, slopes for z-score are 0.06 for PrEP-exposed and -0.06 for PrEP-unexposed (slope difference=0.12, $p<0.001$); for length, z-score are 0.24 for PrEP-exposed and -0.04 for PrEP-unexposed (slope difference=0.27, $p<0.001$).

Table 1.

Pregnancy outcomes among women exposed and unexposed to PrEP

	<i>PrEP-exposed</i>	<i>PrEP-unexposed</i>	<i>Odds Ratio 95% CI p-value</i>	<i>Adjusted Odds Ratio 95% CI p-value</i>
Number of pregnancies	30	96		
Number of women reported pregnancy	30	88		
Number of pregnancies ending with live births	25 (83.3%)	65 (67.7%)		
Number of pregnancies ending in pregnancy loss *	5 (16.7%)	20 (23.5%)	0.42 (0.15–1.19) p=0.103	0.59 (0.15–2.23) p=0.434
Preterm delivery (live births) **	0 (0%)	5 (7.7%)	0.37 (0–2.11) p=0.376	0.54 (0–3.27) p=0.608
Any anomaly (live-born infants) ***	0 (0%)	5 (7.7%)	0.37 (0–2.11) p=0.376	0.57 (0–3.43) p=0.640

* Generalized estimating equation was used to estimate the association between PrEP exposure and pregnancy loss; adjusted OR controls for maternal age at study enrollment, history of pregnancy loss and preterm delivery

** Exact logistic regression was used to evaluate the association between PrEP exposure and pregnancy loss; adjusted OR controls for maternal age at study enrollment, and history of pregnancy loss.

*** Exact logistic regression was used to evaluate the association between PrEP exposure and pregnancy loss; adjusted OR controls for maternal age at study enrollment, and history of pregnancy loss and preterm delivery, and smoking or using alcohol during pregnancy