Pregnancy outcomes following self-reported and objective-measured exposure to oral preexposure prophylaxis in South Africa

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Objective: To compare pregnancy outcomes using self-reported and objective levels of intracellular tenofovir diphosphate (TFV-DP) in pregnant women using preexposure prophylaxis (PrEP).

Design: We enrolled pregnant women >15 years without HIV at first antenatal care visit in an observational cohort study to compare pregnancy outcomes by PrEP use.

Methods: Exposure defined as: any PrEP use [tenofovir disoproxil and emtricitabine (TDF/FTC]) prescription + reported taking PrEP], or objectively-measured TFV-DP in dried blood spots in PrEP-using pregnant women. The primary outcome was a composite of pregnancy loss, preterm birth (<37weeks), low birthweight (<2500 g), small for gestational age ([SGA] ≤ tenth percentile), or neonatal death. Multivariable logistic regression models evaluated individual and composite adverse outcomes by self-reported or objectively measured PrEP use adjusting for age, gestational age, gravidity and socio-economic status.

Results: Between August 19 and February 23, we followed 1195 pregnant women and ascertained 1145 pregnancy outcomes (96%); 72% ($n = 826$) reported taking PrEP while pregnant, 16% did not take PrEP ($n = 178$), 12% were unconfirmed ($n = 141$). Overall, 94.5% ($n = 1082$) had singleton live births with a median birthweight of 3.2 kg [interquartile range (IQR) = 2.9–3.5], with no difference in pregnancy loss between self-reported PrEP exposed vs. unexposed [4.0 vs. 5.6%; adjusted odds ratio (aOR) = 0.65, 95% confidence interval (CI) = 0.32–1.47]. Composite adverse outcomes did not differ by reported PrEP use (20% for both groups; aOR = 1.07, 95% CI = 0.71–1.63). Comparing objective PrEP use (any TFV-DP vs. no TFV-DP or not on PrEP), adverse outcomes did not differ (aOR = 0.64, 95% CI = 0.39–1.04), nor did other outcomes including preterm birth nor SGA.

Conclusions: Pregnancy outcomes did not differ by PrEP exposure (self-reported or objective), suggesting real-world efficacy that TDF/FTC as PrEP is safe in pregnancy.

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Introduction

Pregnant and lactating people (PLP) are at increased risk of acquiring HIV [1] and at elevated risk of vertical HIV transmission when viral loads are elevated [2]. In a national population-based South African evaluation, early vertical HIV transmission was 10.7% for pregnant women who seroconverted in pregnancy [95% confidence interval (CI) = 6.2%, 16.8%] compared with. 2.2% (95% CI = 1.7%, 2.8%) for mothers known to be living with HIV [2,3]. In 2020 alone, roughly 120 000 pregnant or breastfeeding women became newly infected in sub-Saharan Africa, according to UNAIDS estimates [4]. PLP who seroconvert during pregnancy or lactation are at highest risk of vertical HIV transmission and an estimated 45% of new paediatric HIV cases are attributed to incident maternal HIV infection [3,5,6].

Daily oral preexposure prophylaxis (PrEP) TDF/FTC was introduced in South Africa (SA) in 2016 and guidelines were updated in October 2021 to include PrEP for PLP, as recommended by WHO [7,8]. Comprehensive scale-up of oral TDF/FTC for HIV prevention has expanded to reach PLP without HIV. Concerns have been raised about PrEP use during pregnancy and postpartum periods because of the potential for adverse pregnancy and birth outcomes conceivably resulting from *in utero* antiretroviral exposure [9–11]. Prior studies have evaluated PrEP for safety among PLP without HIV as well as antiretroviral therapy in women living with HIV [12–16]. A recent randomized control trial of $n = 540$ pregnant women comparing immediate to delayed PrEP use in pregnant women found that PrEP was not associated with preterm birth nor small for gestational age (SGA) [17]. The risk difference for preterm birth was −4.7% (90% CI = −10.7, 1.2), 2.5% for low birthweight, and 0.9% for SGA; all limits exceeded the noninferiority margin [17]. However, the study's exposure was based on randomization to PrEP (not actual use) and was underpowered.

Existing insights into the possible effect of PrEP use on pregnancy outcomes face significant limitations in their reliance on self-reported use. To date, exposure has been measured using self-reported recent adherence or pill counts [17–19], which may result in an over or under-reporting of actual use and drug exposure. Potential nondifferential misclassification of exposure can lead to underestimation of the true measure of effect [20]. Future studies using objective measures of PrEP exposure in PLP are needed to advance knowledge of safety and effectiveness of TDF/FTC as PrEP in PLP. To our knowledge, our study is the first to evaluate pregnancy and birth outcomes in a large cohort of pregnant women using both objective levels of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) in addition to subjective, self-reported PrEP use.

Methods

Study design and setting

We conducted a prospective cohort study which enrolled consenting pregnant, adolescent girls and women (age > 15 years) without HIV at their first antenatal clinic (ANC) visit. We followed participants through 12-months postpartum. We recruited from one public health clinic in a peri-urban township in Cape Town, Western Cape. The clinic serves as a public health routine service site, Midwife Obstetric Unit, and primary care facility operated by the Government, serving approximately 350 000 individuals with an estimated antenatal HIV prevalence of 30% [21].

Study participants and procedure

The study recruitment began in August 2019 and concluded in October 2021. Study follow up continued through February 2023. The study protocol has been described elsewhere [22]. Briefly, participating individuals were required to have: confirmed HIV-negative by a fourth generation antigen/antibody HIV test, confirmed pregnancy status, intention to stay in Cape Town through 12-months, and absence of contraindications to PrEP. Women 16–17 years old were eligible to enroll in the study as emancipated minors per national guidance on research participation for adolescents. Healthcare providers at study facility provided group counselling to all pregnant women attending antenatal clinic, which included information on HIV testing, prevention of HIV vertical transmission, and the importance of HIV prevention for women without HIV.

Participants received PrEP counselling from trained study staff and surveys were conducted by study interviewers. Women were counselled to continue with PrEP, condom use and other HIV prevention methods (including partner testing and STI testing/treatment), regardless of recent sexual activity or condom use. As previously described [22,23], women were offered aetiological testing for *C. trachomatis*, *N. gonorrhoeae* and *T. vaginalis* at enrolment study visit. All women with a positive STI test result received treatment in line with the South African National guidelines [24]. Participants were followed antenatally for one to four study visits, depending on the gestational age at enrolment, and

postnatally for up to 12 months. The participants were reimbursed 120 South African Rand (~US$8) in grocery vouchers for their time and effort in the study, as well as remuneration for transportation costs. We enrolled $n = 1195$ eligible pregnant women in the study.

Data collection and management

At each visit participants received individual counselling about HIV prevention, including daily oral PrEP. Data collected included maternal demographics, pregnancy history and healthcare information using REDCap [25]. If the participant decided to start PrEP at any visit, the study nurse provided the participant with a one-month supply of TDF/FTC and an invitation card to return in one month for follow-up testing (after which participants received a three-month prescription to correspond with quarterly study follow-up visits). For this study, we restricted analysis to participants who had available pregnancy or birth outcomes.

Study definitions

For this analysis, exposure to PrEP was defined in two ways:

(1) Any PrEP use during pregnancy, defined as receipt of TDF/FTC prescription during pregnancy and self-reported to have taken any PrEP whilst pregnant.
(2) Tenofovir diphosphate (TFV-DP) present in dried blood spots (DBS) among women who reported taking PrEP in the last 30-days, measuring cumulative PrEP adherence over several weeks using erythrocyte intracellular TFV-DP levels detected by liquid chromatography and mass-spectroscopy [26]. We defined objective PrEP use as: any TFV-DP detected DBS results during pregnancy among those on PrEP vs. unquantifiable levels, and categorical TFV-DP detected as below the limit of quantification (BLQ) compared with <2 days/week, 2–6 doses/week and ~7 doses/week in pregnancy [27].

Pregnancy and obstetric outcomes

The study abstracted pregnancy and infant outcome data from women who returned in postpartum for study visits using maternal case files and infant Road to Health cards. For those who did not return (censored, lost to follow up or moved), pregnancy and obstetric outcomes were abstracted from obstetric records and maternity case records at clinics or hospitals throughout Western Cape. Birth anthropometrics were abstracted from the child Road to Health Booklets at the 7-day postpartum visit where mother-infant pairs were evaluated by study teams. Maternal case records and child Road to Health cards are generally complete, yet may have errors noted by providers in birthweight, etc. If pregnancy loss was reported telephonically, gestational age at event may be incorrect or missing.

Gestational age was estimated based on the date of the last menstrual period or ultrasound dating recorded in the maternity case records at first antenatal care visit. Miscarriage or pregnancy loss was defined as noninduced pregnancy loss ≤20 weeks of gestation. Stillbirth was defined as delivery of a baby with no sign of life ≥20 weeks of gestation, including foetal demise. Neonatal mortality was defined as death of a newborn in the first 28 days of life. Preterm live birth was defined as birth before completion of 37 weeks of gestation. Low birthweight was defined as birthweight < 2500 g. In singleton births, the INTERGROWTH-21st Project Standards was used to calculate birthweights ≤10th percentile for gestational age, classified as small for gestational age (SGA); between 10th and 90th percentiles were classified appropriate for gestational age (AGA); and ≥90th percentile were classified large for gestational age (LGA) [28]. WHO guidelines were used to categorize adverse birth outcomes [29]. The primary outcome of interest was composite adverse outcomes, which included pregnancy loss (miscarriage or stillbirth), neonatal death, and singleton births reported as preterm, low birthweight, or SGA. Separate logistic regression models evaluated outcomes by exposure: self-reported PrEP use after prescription, or TFV-DP during pregnancy (analysed as continuous, categorical [27] [BLQ, <2 doses/week, 2–6 doses/week, ~7 doses/week], and binary (any vs. none) in pregnant women reporting PrEP use in past 30 days). Models adjusted for maternal age, gestational age at baseline, gravidity, and socio-economic status (composite of maternal education, employment, income, home type and assets). We included gestational age at baseline for a proxy of time in study and time on PrEP.

Imputation process

We imputed missing pregnancy outcome data in supplementary analyses. After removing nonsingleton preterm births, a total sample of $n = 1138$ of 1145 was used. To assess whether the missing variable was suitable for imputation, all available variables were individually regressed onto each of the missing variables of interest using univariable logistic regression with the outcome of captures vs. missing; infant birthweight (missing, $n = 13$ of 1138, 1%), SGA (missing, $n = 16$ of 1138, 1%) and self-reported PrEP exposure (missing, $n = 140$ of 1138, 12%). Explanatory variable with P-values <0.05 were suggestive of missing at random, and these significant variables were used to impute each of the missing variables respectively (Tables 1 and 2, Supplemental Digital Content, http://links.lww.com/QAD/C979).

A method of multivariate imputation by chained equations (MICE) was used for the imputation processes. For each missing variable within the MICE function, logistic regression was applied for self-report PrEP exposure, while Bayesian linear regression was applied for baby weight at birth. A set of 100 imputed data sets

were created. The imputed infant birthweight were bound between 0 to 7 kg. The pooled dataset was used to perform logistic regression to obtain the effect estimates in Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C979.

For participants in which no DBS were taken or analysed (due to budgetary restrictions), a logical inference was made to explore the possible reason for missingness. In the first scenario of extrapolation, participants who self-reported no PrEP exposure during pregnancy or those who received PrEP during pregnancy but did not return for a follow-up visit to confirm they started PrEP while pregnant, were considered as 'Not on PrEP' or 'No TFV-DP Present'. Alternatively, those who had received PrEP during pregnancy and self-reported PrEP use (without a biomarker collected and analysed) were considered as 'On PrEP' or 'Any TFV-DP Present', thus, increasing numbers in both the exposed to PrEP group and the reference group (Table 4).

Ethics

The PrEP-PP study was approved by the Human Research Ethics Committee at the University of Cape Town (#297/2018) and by the University of California, Los Angeles Institutional Review Board (IRB#18-001622). Written informed consent was provided by all participants in English or isiXhosa.

Results

Baseline characteristics

Between August 2019 and October 2021, we enrolled 1195 pregnant women and 96% ($n=1145$) had an ascertained pregnancy or birth outcome rendering them eligible for analysis. Of the 1145 women, 72% ($n=826$) confirmed PrEP use during pregnancy (prescription received and self-reported having taken PrEP) and 16% ($n=178$) never used PrEP during pregnancy (no prescription or self-report of having taken PrEP), whereas 12% ($n=141$) had an unconfirmed PrEP exposure (received prescription but did not return to ascertain if they ever took PrEP). Women who had more than one previous pregnancy were more likely to receive a PrEP prescription during pregnancy (67 vs. 56%, $P=0.017$).

The median age of participants was 26 years [interquartile range (IQR): 23–31] and the median gestational age at baseline was 21 weeks (IQR: 15–31). Almost all women (97%) reported being sexually active during pregnancy with 3% ($n=36$) reporting more than one partner in the past 3-months. Among women who reported being in a sexual relationship in the past 3-months, 72% reported condomless sex. Almost one-third of women (29%) reported having a partner who was either living with HIV or of unknown serostatus. (Table 1). One woman seroconverted around labour and delivery and was included in this analysis as she was censored after her seroconversion was identified.

Pregnancy and birth outcomes by self-reported preexposure prophylaxis use

Among the 1145 for which we had ascertained pregnancy and birth outcomes, 94.5% ($n=1082$) had a live birth with a median birthweight of 3.2 kg (IQR: 2.9–3.5). Overall, 5.5% of women experienced pregnancy loss ($n=63$), including 3.1% ($n=36$) miscarriages ($\leq$20 weeks' gestation), 2.2% ($n=25$) stillbirths (>20 weeks' gestation), and 0.2% ($n=2$) terminations of pregnancy. Among live births, 8.4% were preterm births ($n=91$) and 10.2% ($n=110$) were low birth weight (<2500 g). Overall, 8.8% ($n=96$) were SGA: 8% were SGA among those born full term ($n=87$) and 0.8% ($n=9$) were SGA among those born preterm (Table 2).

In those with self-reported PrEP use in pregnancy compared to those who did not report PrEP use in pregnancy ($n=1004$), there were no observable differences in pregnancy or birth outcomes in crude and adjusted analyses. Pregnancy loss (defined as miscarriage, stillbirth or neonatal death in analyses) did not differ between women with and without self-reported PrEP use exposure, 4% ($n=33$) vs. 5.6% ($n=10$) (aOR = 0.65, 95% CI = 0.32, 1.47; $P=0.3$). Similarly, preterm delivery did not differ among women with self-reported PrEP exposure during pregnancy compared to those without (8.2% vs. 6.2%, respectively; aOR 1.17, 95% CI = 0.62, 2.40; $P=0.6$). Among all singleton live births, there was no statistical difference detected for babies born SGA between women with and without self-reported PrEP exposure during pregnancy (9 vs. 7%, respectively; aOR for SGA vs. AGA/LGA = 1.58, 95% CI = 0.86, 3.13; $P=0.2$). Composite adverse outcomes included pregnancy loss, preterm delivery, SGA or neonatal death. The overall proportion with an adverse outcome was 20% in the self-report exposed or unexposed groups (aOR = 1.07, 95% CI = 0.71, 1.63; $P=0.8$) (Table 3).

Pregnancy and birth outcomes by objective levels of TDF/FTC

In a subset of pregnant women who returned for a 3- or 6-month study visit during pregnancy and reported any PrEP use in the past month we collected DBS for TFV-DP (analysed within the first 15 months of the study). We compared those with TFV-DP assessment to those who did not return to the study visit or did not report adherence to PrEP and found that the factors that differed included maternal age, PrEP start date, gravidity and gestation age at baseline ($P<0.05$; Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C979).

Comparing pregnant women with any TFV-DP in DBS ($n=181$; 39%) to those with no TFV-DP or not on PrEP during pregnancy ($n=290$; 61%) across the entire period of observation, 96% had live births in the adherent group

Table 1. Baseline characteristics of pregnant women offered preexposure prophylaxis in antenatal care in Cape Town, South Africa between August 2019 and October 2021.

	All women, *N* (%)	Received PrEP prescription, *n* (%)	Did not receive PrEP in pregnancy, *n* (%)	*P*-value
Sociodemographic characteristics	**1195 (100)**	1080 (90)	115 (10)	
Maternal age (median, IQR) years	**26 (23–31)**	26 (23–31)	25 (22–31)	0.3
GA at booking (median, IQR) weeks	**21 (15–31)**	21 (15–30)	23 (13–33)	0.6
Creatinine at booking (median, IQR) μmol/l	**46 (41–52)**	46 (41–52)	46 (40 – 49)	0.6
BMI at booking (median, IQR) kg/m^2	**31 (26–36)**	31 (26–36)	31 (27–35)	> 0.9
Gravidity				**0.017**
1	**405 (34)**	354 (33)	51 (44)	
≥2	**790 (66)**	726 (67)	64 (56)	
Family planning prior to current pregnancy			0.3	
No contraception	**777 (65)**	695 (64)	82 (71)	
Occasional contraception	**325 (27)**	301 (28)	24 (21)	
Using contraception	**93 (8)**	84 (8)	9 (8)	
Education level completed				0.2
Some primary	**7 (1)**	5 (1)	2 (2)	
Primary	**574 (48)**	521 (48)	53 (46)	
Secondary or tertiary	**614 (51)**	554 (51)	60 (52)	
relationship with father of child				> 0.9
Married/cohabiting	**450 (38)**	407 (38)	43 (37)	
Not married nor cohabiting	**745 (62)**	673 (62)	72 (63)	
Employment status				0.7
Full-time employment	**313 (26)**	286 (26)	27 (23)	
Part-time employment	**116 (10)**	103 (9)	13 (11)	
Unemployed or attending school/college	**766 (64)**	691 (64)	75 (65)	
Socioeconomic status (SES)				0.3
Low SES	**381 (32)**	349 (32)	32 (28)	
Moderate/high SES	**814 (68)**	731 (68)	83 (72)	
Personal monthly income				0.8
None	**657 (55)**	594 (55)	63 (55)	
<$100	**118 (10)**	104 (10)	14 (12)	
$100–350	**329 (27)**	300 (28)	29 (25)	
$351+	**91 (8)**	82 (7)	9 (8)	
Psychosocial characteristics				
EPDS threshold				0.3
Below threshold <11	**1106 (93)**	996 (92)	110 (96)	
Above threshold ≥11	**89 (7)**	84 (8)	5 (4)	
Alcohol use during current pregnancy	**72 (6)**	68 (6)	4 (3)	0.3
Ever experienced IPV	**147 (12)**	137 (13)	10 (9)	0.3
Any STI at enrolment (CT/NG/TV)				>0.9
Positive	**373 (31)**	338 (31)	35 (30)	
Negative	**822 (69)**	742 (69)	80 (70)	
Partner's serostatus				0.4
Concordant HIV-negative	**849 (71)**	763 (71)	86 (75)	
Serodiscordant or unknown	**346 (29)**	317 (29)	29 (25)	
HIV risk perception at enrolment				>0.9
No chance at all	**650 (54)**	587 (54)	63 (55)	
Some/high chance	**545 (46)**	493 (46)	52 (45)	
Sexual behaviour in the past 3 months				
Number of sex partners				0.8
No sex partner	**33 (3)**	29 (3)	3 (3)	
1 sex partner	**1126 (94)**	1018 (94)	108 (94)	
2+ sex partners	**36 (3)**	33 (3)	3 (3)	
Condom use during sex				0.5
Sometimes/always	**298 (25)**	271 (25)	27 (23)	
Never/rarely	**864 (72)**	780 (72)	84 (73)	
No sex partner	**33 (3)**	29 (3)	4 (4)	
Prior knowledge of PrEP	**321 (27)**	288 (27)	33 (29)	0.7
PrEP initiation at baseline				**<0.001**
Did not initiate PrEP at baseline	**186 (16)**	71 (7)	115 (100)	
Initiated at baseline	**1009 (84)**	1009 (93)	0 (0)	

ANC, antenatal care; GA, gestational age; IPV, intimate partner violence; IQR, interquartile range; *n*, number of participants; PrEP, preexposure prophylaxis; SD, standard deviation.

Table 2. Pregnancy and birth outcomes of women ever exposed compared to women never exposed to PrEP during pregnancy ($n = 1145$ women with confirmed and unconfirmed PrEP exposure measures and known pregnancy outcomes).

	All women, *N* (%)	PrEP exposed (self-report), *n* (%)	PrEP unexposed (self-report), *n* (%)	Unconfirmed PrEP exposure (no self-report), *n* (%)
Total of all women with pregnancy outcomes	**1145 (100)**	**826 (72)**	**178 (16)**	**141 (12)**
Pregnancy losses				
Total pregnancy losses	63 (5.5)	27 (3.3)	10 (5.6)	26 (18.4)
Miscarriage GA ≤20 weeks	36 (3.1)	11 (1.3)	5 (2.8)	20 (14.2)
Stillbirth GA >20 weeks	25 (2.2)	14 (1.7)	5 (2.8)	6 (4.2)
Termination of pregnancy	2 (0.2)	2 (0.2)	0 (0)	0 (0)
Live birth outcomes				
Total live births	**1082 (94.5)**	**799 (96.7)**	**168 (94.4)**	**115 (81.6)**
Full term delivery GA ≥37 weeks	991 (91.6)	731 (91.4)	157 (93.5)	103 (89.6)
Preterm delivery GA <37 weeks	91 (8.4)	68 (8.5)	11 (6.6)	12 (10.4)
Neonatal death	6 (0.6)	6 (0.8)	0 (0)	0 (0)
LBW< 2500 g	110 (10.1)	85 (10.6)	15 (8.9)	10 (8.7)
Birth weight (median, IQR) grams	3.2 (2.9–3.5)	3.2 (2.9–3.5)	3.3 (2.9–3.6)	3.3 (2.9–3.5)
Gestational age at birth (median, IQR) weeks	39 (38–40)	39 (38– 40)	39 (38–40)	39 (36.8–40)
Full term gestational percentiles				
SGA (≤10th percentile)	87 (8)	67 (8.4)	11 (6.6)	9 (7.8)
AGA (>10th and <90th percentile)	767 (70.8)	567 (71)	129 (76.8)	71 (61.7)
LGA (≥90th percentile)	107 (9.8)	79 (9.9)	17 (10.1)	11 (9.6)
Preterm gestational percentiles				
SGA (≤10th percentile)	9 (0.8)	7 (0.9)	1 (0.6)	1 (0.9)
AGA (>10th and <90th percentile)	60 (5.5)	48 (6)	6 (3.6)	6 (5.2)
LGA (≥90th percentile)	14 (1.3)	8 (1)	3 (1.9)	3 (2.6)
Composite adverse outcome				
Adverse outcome	250 (21.8)	169 (20.5)	35 (19.7)	46 (32.6)
No adverse outcome	895 (78.2)	657 (79.5)	143 (80.3)	95 (67.4)

AGA, appropriate for gestational age; GA, gestational age; IQR, interquartile range; LBW, low birthweight; LGA, large for gestational age; PrEP, preexposure prophylaxis; SGA, small for gestational age. Composite adverse outcome includes all miscarriage, stillbirth, neonatal death, preterm birth, and SGA.

vs. 90% in the not on PrEP and nonadherent group (aOR for any TFV-DP in DBS vs. none = 2.99, 95% CI = 1.33, 7.67; $P = 0.013$) (Table 4). Preterm birth did not differ among infants born to women with or without quantifiable TFV-DP levels in DBS (6.6 vs. 6.9%, respectively; aOR = 0.97, 95% CI = 0.44, 2.03; $P \geq 0.9$). Infants SGA were also similar in both groups (6.6% vs. 7.2%, respectively, aOR = 0.83; 95% CI = 0.38, 1,78; $P = 0.6$). Stillbirth occurred in $n = 4$ (2.2% of $n = 181$) of infants born to women with TFV-DP in their DBS compared to $n = 8$ (2.8% of $n = 290$) in women not on PrEP or without TFV-DP present (aOR = 0.83, 95% CI = 0.21, 2.80; $P = 0.8$). Neonatal death occurred in $n = 1$ (0.5% of $n = 181$) infant born to a woman with TFV-DP present in pregnancy and did not occur among those without PrEP. Overall, 17% of women with TFV-DP detectable in their pregnancy had an adverse pregnancy or birth outcome, compared to 23% in women not on PrEP or with undetectable TFV-DP in DBS (aOR = 0.64, 95% CI = 0.39, 1.04; $P = 0.075$) (Fig. 1).

There were no significant differences in pregnancy or birth outcomes by TFV-DP level (any vs. none, continuous TFV-DP, nor categorical definition of TFV-DP

Table 3. Unadjusted and adjusted association between self-reported PrEP intake during pregnancy (confirmed only) and adverse birth outcomes between August 2019 and October 2021 ($N = 1004$ women with pregnancy and birth outcomes and PrEP exposure confirmation).

Outcome measure	Predictor (*n*, %)	*N*	Odds ratio (95% CI), *P*-value	Adjusted odds ratio^ (95% CI), *P*-value
Preterm delivery (<37 weeks)[a]	PrEP unexposed ($n = 11$, 6.2%)	178	Ref	Ref
	PrEP exposed ($n = 62$, 8.2%)	820	1.24 (0.67–2.54), 0.5	1.17 (0.62–2.40), 0.6
SGA (≤10th percentile)[a]	PrEP unexposed ($n = 12$, 7%)	177	Ref	Ref
	PrEP exposed ($n = 76$, 9%)	811	1.42 (0.78–2.80), 0.3	1.58 (0.86–3.13), 0.2
Pregnancy loss[b]	PrEP unexposed ($n = 10$, 5.6%)	178	Ref	Ref
	PrEP exposed ($n = 33$, 4%)	826	0.70 (0.35–1.52), 0.3	0.65 (0.32–1.47), 0.3
Composite adverse outcome[c]	PrEP unexposed ($n = 35$, 20%)	178	Ref	Ref
	PrEP exposed ($n = 169$, 20%)	826	1.05 (0.71, 1.60), 0.8	1.07 (0.71, 1.63), 0.8

CI, confidence interval; PrEP, preexposure prophylaxis.
[a]In singleton live births.
[b]Pregnancy loss includes miscarriage, stillbirth and neonatal death; excluding termination of pregnancy.
[c]Composite adverse outcome includes miscarriage, stillbirth, neonatal death, preterm delivery and SGA.
^Adjusted for: maternal age at baseline, gestational age at baseline, gravidity and socio-economic status.

Table 4. Unadjusted and adjusted associations between objective PrEP use in pregnancy (any adherence vs. nonadherence or not on PrEP) and pregnancy and birth outcomes.

	On PrEP in pregnancy: any TDF-DP present in DBS, *n* (%)	Not on PrEP in pregnancy: no TFV-DP present, *n* (%)	OR[b] (95% CI), *P*-value	aOR[a,b] (95% CI), *P*-value	aOR[a,c] (95%, CI), *P*-value
Total	181 (39)	290 (61)	On PrEP ($n=181$) Not on PrEP ($n=290$)	On PrEP ($n=181$) Not on PrEP (n=290)	On PrEP ($n=701$) Not on PrEP ($n=290$)
Live birth	174 (96)	262 (90)	2.66 (1.20, 6.73), 0.024	2.99 (1.33, 7.67) 0.013	2.00 (1.15, 3.46), 0.013
Preterm (<37 weeks)	12 (6.6)	20 (6.9)	0.96 (0.44, 1.99), > 0.9	0.97 (0.44, 2.03), >0.9	1.37 (0.82, 2.38), 0.2
SGA (≤10th percentile)	12 (6.6)	21 (7.2)	0.80 (0.37, 1.65), 0.6	0.83 (0.38, 1.78), 0.6	1.21 (0.73, 2.08), 0.5
Pregnancy loss	7 (3.9)	28 (9.7)	0.38 (0.15, 0.84), 0.024	0.33 (0.13, 0.75), 0.013	0.50 (0.29, 0.87), 0.013
Miscarriage	2 (1.1)	20 (6.9)	0.15 (0.02, 0.53), 0.011	0.13 (0.02, 0.48), 0.008	0.22 (0.10, 0.48), <0.001
Stillbirth	4 (2.2)	8 (2.8)	0.80 (0.21, 2.57), 0.7	0.83 (0.21, 2.80), 0.8	0.72 (0.30, 1.85), 0.5
Neonatal death	1 (0.6)	0 (0)			
Composite adverse pregnancy or birth outcomes	31 (17)	67 (23)	0.69 (0.42, 1.10), 0.12	0.64 (0.39, 1.04), 0.075	0.99 (0.71, 1.38), > 0.9

aOR, adjusted odds ratio; CI, confidence interval; PrEP, preexposure prophylaxis.
[a]Adjusted for: maternal age at baseline, gestational age at baseline, gravidity and SES.
[b]Allocated participants who had no TFV-DP in DBS & never reported taking PrEP to 'Not on PrEP in pregnancy' category.
[c]Allocated participants who started PrEP but did not have DBS drawn or analysed, or those missing self-report data to 'On PrEP in pregnancy'.

[comparing BLQ, <2 doses/week, 2–6 doses/week and ~7 doses/week) (data not tabled). Further, in sensitivity analyses in which we allocated those who started PrEP but did not have analysis of DBS or did not return for a study visit to evaluate their self-reported PrEP use ($n=520$ additional women) to the 'On PrEP' group, there were no differences in effect estimates (Table 4).

Finally, the imputation of self-reported data and missing birth outcomes yielded similar proportions of PrEP exposed vs. PrEP unexposed as the confirmed self-reported data (Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C979). Both the confirmed and imputed self-reported tables present data with similar direction and magnitude of crude and adjusted associations ($P>0.05$).

Discussion

To our knowledge, this was the first study comparing the safety of TDF/FTC among pregnant women using

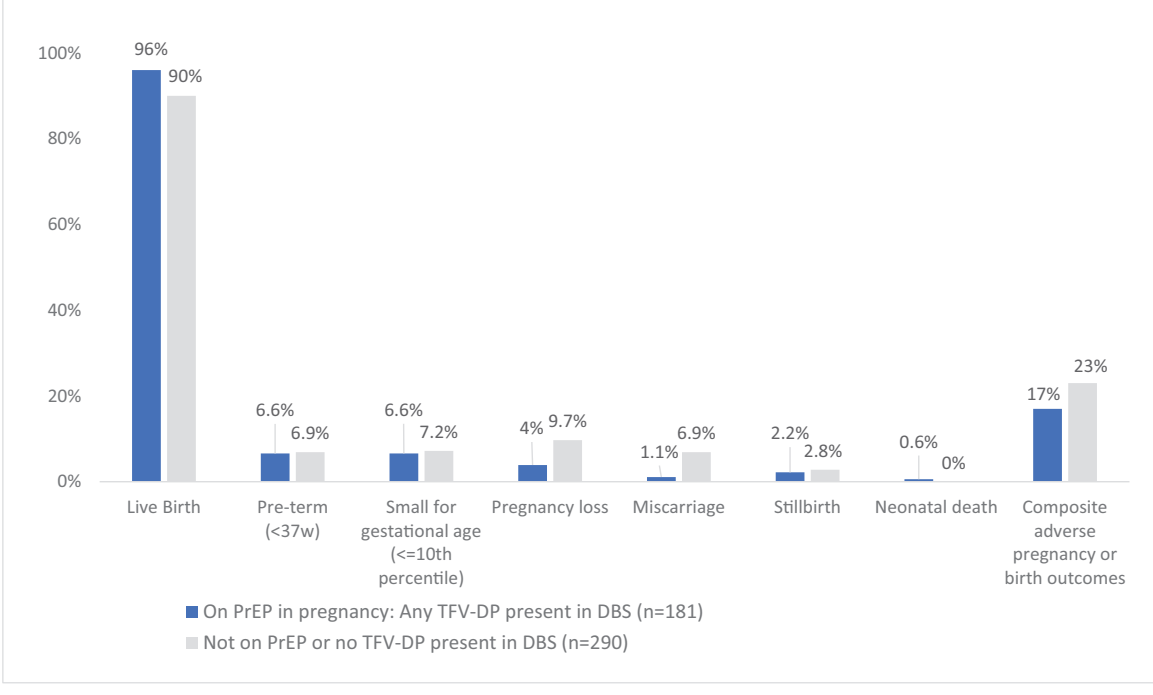

Fig. 1. Pregnancy and birth outcomes in pregnant women who reported taking oral PrEP during pregnancy by TFV-DP level (any vs. none or not on PrEP in pregnancy; $n=471$).

objective levels of TFV-DP in DBS compared to self-reported PrEP adherence. We found that the initiation of PrEP in pregnancy among those who received a prescription for PrEP and reported taking PrEP, as well as among those who had TFV-DP levels of PrEP in their blood during pregnancy, were not associated with pregnancy loss, preterm birth, low birthweight, small for gestation age infants or neonatal death, nor the composite adverse birth outcome.

Our novel approach to evaluating objective levels of TDF/FTC use and self-reported PrEP use in an observational, nonrandomised study demonstrates that regardless of how PrEP use is estimated, objectively or subjectively, its use does not appear to have a statistically significant association with negative maternal or infant outcomes. Given prior awareness that TFV-DP levels during pregnancy may be somewhat reduced [27,30], further investigations may be useful in filling the gap of knowledge regarding minimum protective efficacy of PrEP with respect to safety outcomes during pregnancy. Women who took PrEP may be healthier than those who did not take PrEP, which may bias results towards the null in an observational study; though we have demonstrated that PrEP use was not exclusive to healthier women within our study sample (Table 1).

Previous studies of TDF/FTC as PrEP measuring exposure using self-reported adherence [18], or randomization to start PrEP in pregnancy vs. delayed PrEP in postpartum period [17], may over-estimate PrEP use and could result in nondifferential exposure misclassification, biasing results towards the null or underestimating the true measure of effect of PrEP on pregnancy outcomes [20].

Our previous publication in the same study demonstrated that neither self-reported PrEP use nor prescription provides an accurate reflection of true use [31]. Inconsistencies in adherence estimates between objective and self-reported measures support findings of prior studies which suggest that self-reported use may be an unreliable tool for assessment of exposure [32]. Of pregnant women in antenatal care within our study who reported taking PrEP in the past 30 days, only 39% had any TFV-DP in their DBS, the remainder of participating women reporting PrEP use in the past month had levels below limits of quantification, demonstrating that objectively measured adherence to PrEP was low overall and did not correlate with self-reported use [31].

Our study demonstrates similar results to a recent randomized control trial of PrEP in pregnancy that found no differences with preterm birth or SGA infants in SA [17]. This study found that the prevalence of preterm births and very preterm births based on ultrasonographic measure of gestation was not statistically different those women randomized to TDF/FTC during pregnancy vs. delayed PrEP start (risk difference = −5.6%, 95% CI = −12.1–0.1). These results are similar to another analysis of perinatal outcomes following PrEP exposure in an observational study in Kenya [18].

Overall findings demonstrate the need for pregnancy-specific strategies addressing how to best monitor effective PrEP use and further incorporate counselling of effective use emphasizing the safety of PrEP in antenatal settings. As utilization of oral PrEP continues to unfold globally, future studies may employ alternative, objective measurements of use, such as hair, plasma or urine TFV levels, which may allow for increased accuracy of findings pertaining to safety and adherence, as well as improved evaluations of longer- or shorter-term PrEP use among PLP [32].

Our study has several limitations. Firstly, levels of PrEP adherence were generally low, and if there were a dose-response relationship one might expect to observe a significant effect only in cohorts with better adherence; further our study is limited because self-reported PrEP was significantly higher than objective PrEP levels in TFV-DP, limiting the utility of findings by self-reported PrEP use. Secondly, we used a smaller sub-set of women who reported taking PrEP and returned for a study visit for the TFV-DP analysis, which may bias towards a healthier population that gave birth to live infants. Thirdly, we included a limited period for TFV-DP analysis in pregnancy, which did not enable us to establish PrEP use during entire pregnancy, just a proxy in 2nd or 3rd trimester, potentially resulting in an over or under-estimate of true PrEP use. A sampling bias may arise if healthier women continued on PrEP compared with those who did not continue on PrEP, and birth outcomes could underestimate early pregnancy loss due to collection of routine data. Fourthly, not all women in the study had an ultrasonographic measure of gestation which may have affected our observed outcomes, including preterm birth and SGA. In addition, our study excluded women who planned to relocate in the postpartum period, which may bias towards a different socio-demographic profile. Finally, generalizability of results may be limited due to recruitment being exclusively from one urban clinic in Cape Town.

Conclusion

Our study presents one of the first analyses to use objective measures of PrEP use in pregnancy as well as self-reported use to evaluate safety of oral TDF/FTC use in pregnancy. Pregnancy and birth outcomes did not differ by PrEP exposure, whether self-reported or objectively assessed. Our study suggests real-world efficacy that oral TDF/FTC as PrEP is safe during pregnancy and highlights the importance of counselling pregnant women on its effective use and safety.

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Conflicts of interest

There are no conflicts of interest.

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