Maternal and pregnancy outcomes in women initiating and declining PrEP during pregnancy: the IMPAACT 2009 study

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BACKGROUND

Pregnancy represents a period of high risk for HIV acquisition, especially in settings of high HIV prevalence.

Use of daily oral pre-exposure prophylaxis (PrEP) with emtricitabine and tenofovir disoproxil fumarate (FTC-TDF) can reduce horizontal HIV transmission and is recommended for pregnant and postpartum populations.

To date, however, few studies have evaluated uptake, maternal safety, and pregnancy outcomes in the context of a clinical trial.

METHODS

The PrEP Comparison Component of IMPAACT 2009 enrolled pregnant participants aged 16-24 years at <32 weeks gestation in Malawi, South Africa, Uganda, and Zimbabwe. Gestational age was confirmed by ultrasound at time of screening. All participants met local criteria to initiate PrEP.

Participants were enrolled in parallel cohorts based on choice to initiate or decline daily oral FTC-TDF for PrEP at entry. Regardless of their choice at entry, they were permitted to start or stop PrEP at any time during follow-up.

All participants received integrated Next Step Counseling (iNSC) on overall well-being, sexual health, and HIV prevention. While on PrEP, participants also received regular drug level feedback (based on monthly tenofovir diphosphate measurement in collected dried blood spots) and weekly two-way text (i.e., SMS) messaging.

Here, we report safety outcomes through pregnancy and delivery. Adverse events (AEs) were graded per the 2017 DAIDS toxicity tables and assessed for relatedness to FTC-TDF.

AEs per participant (within each category and diagnosis) were reported by highest grade. MedDRA High Level Terms (HLTs) were used for classification.

Adverse pregnancy outcomes included fetal loss (i.e., spontaneous abortion, stillbirth), preterm birth, and small-for-gestational-age by INTERGROWTH-21st standards.

Proportions (with Clopper-Pearson 95% confidence intervals) were calculated for highest-grade AEs through pregnancy outcome by PrEP use.

Our findings suggest that oral FTC-TDF for PrEP is safe during pregnancy. Antenatal programs should offer PrEP as part of routine HIV prevention and support individual decisions about its use over time.

RESULTS

From March to December 2022, 350 eligible participants were enrolled and included in the maternal safety analysis. Of those, 324 participants had complete delivery information recorded and were included in the pregnancy outcome analysis.

Overall, 233 participants initiated PrEP during pregnancy: 229 started at entry and four started later. Median duration of antenatal PrEP use was 11 weeks (IQR: 7.7-15). In contrast, 117 participants declined PrEP at entry and never initiated PrEP during pregnancy (Tables 1 and 2).

A total of 31 (9%) participants experienced at least one grade ≥3 AE through delivery, with a greater proportion among PrEP initiators (11.2%; 95%CI: 7.4-15.9%) vs. decliners (4.3%, 95%CI: 1.4-9.7%; Table 3).

Table 1: Participant characteristics by PrEP uptake at enrollment

	Initiated PrEP at enrollment *n = 229*	Declined PrEP at enrollment *n = 121*
Age, years, median (Q1, Q3)	21 (19, 22)	21 (20, 22)
Weight, kg, median (Q1, Q3)	63.6 (57.0, 70.0)	61.2 (56.9, 66.8)
BMI, kg/m^2, median (Q1, Q3)	24.6 (22.5, 27.3)	24.2 (22.5, 27.5)
Gravidity		
1	156 (68%)	64 (53%)
2	55 (24%)	49 (40%)
3 or greater	18 (8%)	8 (7%)
Gestational age at enrollment, weeks		
Median (Q1, Q3)	24.0 (20.0, 27.0)	25.0 (21.5, 27.0)
First trimester	4 (2%)	2 (2%)
Second trimester	149 (65%)	79 (65%)
Third trimester	74 (33%)	39 (33%)
Missing	2	1
Country		
Malawi	23 (10%)	27 (22%)
South Africa	29 (13%)	11 (9%)
Uganda	54 (24%)	23 (19%)
Zimbabwe	123 (54%)	60 (50%)

Table 2: Time on PrEP

	Initiated PrEP at enrollment *n = 229*	Initiated PrEP after enrollment *n = 4*
PrEP exposure at time of delivery		
On PrEP at delivery	131 (57%)	3 (75%)
Discontinued PrEP prior to delivery	98 (43%)	1 (25%)
Follow-up time prior to initiating PrEP, weeks		
Median (Q1, Q3)	–	7.1 (5.2, 9.1)
Follow-up time prior to stopping PrEP, weeks		
Median (Q1, Q3)	11.3 (7.9, 15.0)	5.1 (2.6, 7.9)

Table 3: Grade 3 and 4 adverse events by PrEP use in pregnancy

	Initiated PrEP during pregnancy *n = 233* GRADE			Declined PrEP during pregnancy *n = 117* GRADE		
	3	4	Total	3	4	Total
Overall	**23 (10%)**	**3 (1%)**	**26 (11%)**	**5 4%)**	**0 (0%)**	**5 (4%)**
Blood and lymphatic system disorder	1 (<1%)	1 (<1%)	2 (<1%)	0 (%)	0 (%)	0 (%)
Anemia	1	1	2	–	–	–
Endocrine disorders	1 (<1%)	0 (%)	1 (<1%)	0 (%)	0 (%)	0 (%)
Hyperprolactinemia	1	–	1	–	–	–
Infections	5 (2%)	0 (0%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)
Amniotic cavity	1	–	1	–	–	–
Bacterial vaginosis	1	–	1	–	–	–
Urinary tract infection	2	–	2	–	–	–
Vulvovaginal candidiasis	1	–	1	–	–	–
Vulvovaginitis	1	–	1	–	–	–
Injury or procedural complications	0 (%)	0 (%)	0 (%)	1 (<1%)	0 (%)	1 (<1%)
Perineal injury	–	–	–	1	–	1
Abnormal laboratory investigations	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Decreased progesterone	1	–	1	–	–	–
Pregnancy, puerperium, and perinatal conditions	19 (8%)	2 (<1%)	21 (9%)	4 (3%)	0 (0%)	4 (3%)
Cephalopelvic disproportion	4	–	4	–	–	–
Eclampsia	–	1	1	–	–	–
Fetal death	1	–	1	2	–	2
Fetal distress syndrome	4	–	4	1	–	1
Fetal malpresentation	1	–	1	–	–	–
Meconium	1	–	1	–	–	–
Oligohydramnios	1	–	1	–	–	–
Placental previa	1	–	1	–	–	–
Postpartum hemorrhage	–	1	1	1	–	1
Premature baby	2	–	2	–	–	–
Premature rupture membranes	1	–	1	–	–	–
Prolonged labor	4	–	4	–	–	–
Stillbirth	1	–	1	–	–	–
Umbilical cord, nuchal	1	–	1	–	–	–
Renal and urinary disorders	1 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Glyosuria	1	–	1	–	–	–

** Overall and categorical tallies (shaded) represent the number and proportion of participants with at least one AE at the stated grade. The specific diagnoses (numbers only) are tallied by occurrence. An individual may have more than one such diagnosis.*

No grade ≥ 3 AEs were deemed related to PrEP by onsite investigators. No participants acquired HIV during pregnancy.

Overall, 79 (24%) participants experienced adverse pregnancy outcomes, with no statistical difference between groups (Table 4).

Table 4: Pregnancy outcome by PrEP use in pregnancy

	Initiated PrEP *n = 233*	Declined PrEP *n = 117*	P-value*
Total with pregnancy outcome data	223	112	
Any adverse outcome	51 (24%)	28 (26%)	0.68
Fetal loss	2 (1%)	4 (4%)	0.10
Total live births	221	108	
Preterm birth <37 weeks	19 (9%)	7 (6%)	0.66
Small for gestational age	34 (16%)	19 (18%)	0.63

* Fisher's exact test

Rates of adverse pregnancy outcomes appeared lower than those observed by Balkus, et al. (PLOS One, 2021) across four countries, including several IMPAACT 2009 sites. In that study, 13.0% experienced a preterm birth (range 10.4-20.7%) and 4.1% a stillbirth (range 3.1-5.5%). These estimates are higher than those observed in IMPAACT 2009.

CONCLUSIONS

Daily oral FTC-TDF remains a safe and essential component of HIV prevention in pregnancy, even as the options for PrEP expand.

A high occurrence of grade ≥ 3 AEs was noted; however, none were thought to be related to PrEP use.

Over 40% of those initiating PrEP stopped by the time they gave birth, reflecting the evolving needs for HIV prevention. Programs should prepare for and support such choices in clinical settings.

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