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BRIEF REPORT

Frequency and Predictors of Tenofovir-diphosphate Detection Among Young Kenyan Women in a Real-world Pre-exposure Prophylaxis Implementation Program

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In a pre-exposure prophylaxis program for Kenyan women, we detected tenofovir-diphosphate in 61% (125/201) of randomly selected dried blood spots collected at the first follow-up visit. Tenofovir-diphosphate was detected more frequently among women who had partners living with human immunodeficiency virus, who were not pregnant, and who were ≥24 years.

Keywords. HIV/AIDS; pre-exposure prophylaxis; adherence; women.

Young women in sub-Saharan Africa have 1 of the highest human immunodeficiency virus (HIV) incidence rates globally, with 6200 new infections per week [1]. New prevention tools, including emtricitabine/tenofovir disoproxil fumarate–based oral pre-exposure prophylaxis (PrEP), can curb the rate of new infections. Thus, PrEP implementation is progressing in regions of Africa with high burdens of HIV, with young women as a priority population. Kenya has led efforts to expand implementation, with >25 000 individuals initiating PrEP as of May 2019 [2], yet few data exist on real-world PrEP adherence among young women in this setting.

The PrEP Implementation for Young Women and Adolescents (PrIYA) program was a 2-year implementation project to reach adolescent girls and young women at high risk for HIV acquisition through the integrated delivery of PrEP within routine maternal child health (MCH) and family planning (FP) clinic systems [3, 4]. PrIYA was conducted in collaboration with the Kisumu County Department of Health and Sanitation and the National AIDS and Sexually Transmitted Infection Control Programme, and was implemented in 16 facilities in Kisumu County, which is a region with an adult HIV prevalence of 19.9% [5]. In PrIYA, a majority of young women with HIV behavioral risk factors accepted PrEP when offered within routine MCH and FP clinics, and approximately 40% persisted with PrEP use beyond 30 days postinitiation [3].

The objective of the current analysis was to evaluate the detection of tenofovir-diphosphate (TFV-DP), an objective biomarker of PrEP adherence, among women who initiated PrEP in the PrIYA Program.

METHODS

The program procedures have been previously described [3]. Briefly, between November 2017 and December 2018, general population women seeking MCH and FP services at 16 facilities were screened for behavioral HIV risk factors and offered PrEP per national guidelines. Routine follow-up visits were scheduled at 1 month and then every 3 months post–PrEP initiation throughout the duration of PrEP use. The protocol complied with Kenya Ministry of Health guidelines and was approved by the Human Subjects Division of the University of Washington, the Kenyatta National Hospital Ethical Review Committee, and the Kisumu County administration and facility managers. Women provided written informed consent for dried blood spot (DBS) collection. TFV-DP concentration results were not returned to participants.

DBS samples were collected by PrIYA program nurses who received standardized training on DBS collection via fingerstick. DBS samples were transported to a centralized -20℃ freezer for storage within a 48-hour window after collection. During the program, DBS collection was scaled up to all 16 program-dedicated sites, and DBS samples were collected at all routinely scheduled PrEP follow-up visits. We randomly selected DBS samples for TFV-DP quantification from 20% of follow-up visits where the clients reported having used PrEP in the last 14 days. We also tested an additional sample from a client who seroconverted to HIV after initiating PrEP; this was the only client to seroconvert during the PrIYA Program.

DBS samples were tested for TFV-DP in red blood cells using validated ultra-performance liquid chromatography–tandem mass spectrometry methods at the University of Colorado [6]. Previous studies demonstrated that DBS samples from fingerstick and venipuncture can be used for TFV-DP quantification [7]. Values below the lower limit of quantification

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for TFV-DP (25 fmol/sample) were considered undetectable [7]. TFV-DP has a half-life of 17 days in red blood cells, and a DBS provides a marker of cumulative adherence over the prior 1–2 months [7]. We evaluated the predictors of detectable TFV-DP (yes/no) among the DBS samples collected at the first follow-up visit scheduled 30 days post–PrEP initiation, using univariate Poisson regression models with robust error variance accounting for clinic clustering. We used descriptive statistics to summarize TFV-DP concentrations ≥500 fmol/punch, which is consistent with ≥4 doses/week in the first month of PrEP use in 75% of individuals, based on directly observed therapy studies among US populations [7].

RESULTS

Overall, 4376 women initiated PrEP in the PrIYA Program (90% from MCH and 10% from FP clinics) and 2156 (49%) attended at least 1 in-person follow-up visit. A total of 5025 in-person follow-up visits were attended during the program, with 2908 after DBS collection began; of those, 1132 (39%) were from visits at which the client reported PrEP use within the prior 14 days and met the inclusion criteria for TFV-DP testing. We randomly selected 233 DBS samples for testing (20% of those that met the inclusion criteria); 1 randomly selected sample was rejected by the laboratory prior to testing. Among the 232 DBS samples with TFV concentrations available, 201 DBS samples were from unique women attending their first PrEP follow-up visit, at a median of 5 weeks (IQR [interquartile range], 4–18) since PrEP initiation; 31 DBS samples were from subsequent visits among the same women, at a median of 24 weeks since PrEP initiation (IQR, 17–37). The median age was 25 years (IQR, 21–30), 24% were pregnant, and a majority (77%) were married. One-fourth (25%) of the women had a partner known to be living with HIV, and condomless sex in the prior 6 months was frequently reported (93%); other behavioral risk factors were infrequently reported (Table 1).

Overall, 153/232 (66%) DBS samples had detectable TFV-DP, with a median concentration of 535 fmol/punch (IQR, 357–719).

Table 1. Characteristics of Clients

		TFV-DP Detection at First Follow-Up Visit			
		Any Detectable TFV-DP, n = 201			
Baseline Characteristics	n	No, n = 76	Yes, n = 125	Risk Ratio (95% CI)	*P* Value
Age					
<24 years	89	45 (50.6%)	44 (49.4%)	ref	
≥24 years	112	31 (27.7%)	81 (72.3%)	1.46 (1.18–1.81)	<.001**
Pregnancy status					
Currently pregnant	49	24 (49.0%)	25 (51.0%)	ref	
Not pregnant	152	52 (34.2%)	100 (65.8%)	1.29 (.99–1.67)	.055*
Marital status					
Not married	46	14 (30.4%)	32 (69.6%)	ref	
Married	155	62 (40.0%)	93 (60.0%)	.86 (.67–1.11)	.246
Male partner HIV status[a]					
Negative	56	34 (60.7%)	22 (39.3%)	ref	
Unknown	94	39 (41.5%)	55 (58.5%)	1.49 (.94–2.35)	.088*
Positive	51	3 (5.9%)	48 (94.1%)	2.39 (1.65–3.48)	<.001**
Condomless sex[b]					
No	15	5 (33.3%)	10 (66.7%)	ref	
Yes	186	71 (38.2%)	115 (61.8%)	.93 (.62–1.38)	.710
Forced to have sex[b]					
No	172	67 (39.0%)	105 (61.1%)	ref	
Yes	9	1 (11.1%)	8 (88.9%)	1.46 (1.10–1.93)	.009**
Experienced IPV[b]					
No	166	63 (38.0%)	103 (62.1%)	ref	
Yes	15	5 (33.3%)	10 (66.7%)	1.07 (.74–1.57)	.710
STI diagnosis[a,b]					
No	196	75 (38.3%)	121 (61.7%)	ref	
Yes	5	1 (20.0%)	4 (80.0%)	1.30 (.92–1.83)	.138
Engaged in transactional sex[b]					
No	196	74 (37.8%)	122 (62.2%)	ref	
Yes	5	2 (40.0%)	3 (60.0%)	.96 (.44–2.13)	.927

Data are shown by TFV-DP detection at first follow-up visit. n = 201. *$P < .10$; **$P < .01$.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IPV, intimate partner violence; STI, sexually transmitted infection; TFV-DP, tenofovir diphosphate.

[a]Self-reported by women.

[b]In the last 6 months.

Among the first follow-up visit DBS samples, 125/201 (62%) had detectable TFV-DP (median concentration of 492 fmol/punch; IQR, 335–718) and 61/201 (30%) had ≥500 fmol/punch. Among DBS samples from later follow-up visits, 28/31 (90%) had TFV-DP detection (median concentration of 635 fmol/punch; IQR, 436–761). There was 1 woman who tested positive as living with HIV during follow-up at 5 weeks post–PrEP initiation; TFV-DP was not detected in the DBS samples collected at seroconversion.

Among the first follow-up visits (n = 201), detectable TFV-DP was more likely among nonpregnant women (66% nonpregnant vs 51% pregnant; risk ratio [RR] = 1.29; $P = .055$; Table 1) and older women (72% of those ≥24 years vs 49% of those <24 years; RR = 1.46; $P < .001$). Among DBS samples with TFV-DP detection, the median concentration was 307 fmol/punch (IQR, 190–438) for pregnant women and 597 fmol/punch (IQR, 398–761) for nonpregnant women. Compared to women who reported having a male partner without HIV, TFV-DP detection was over 2-fold higher among women with partners known to be living with HIV (39% vs 94%, respectively; RR = 2.39; $P < .001$) and was similar for women with partners with an unknown HIV status (39% vs 59%, respectively; RR = 1.49; $P = .088$). A higher likelihood of TFV-DP was also associated with being forced to have sex in the last 6 months (RR = 1.46; $P = .009$).

DISCUSSION

In this programmatic evaluation of PrEP delivery to Kenyan women, two-thirds of randomly selected blood samples had detectable TFV-DP levels. Women who had partners known to be living with HIV, who were not pregnant, and who were ≥24 years old were more likely to have TFV-DP detected. However, the majority of pregnant women, those with partners with an unknown HIV status, and those <24 years old also had detectable levels, and median TFV-DP levels were in the 4 doses/week range based on cohorts from the United States [7]. Our data suggest that African women in PrEP programs who report persisting with daily oral PrEP in the month following initiation have evidence of PrEP exposure. As PrEP implementation advances, more strategies for monitoring and enhancing adherence in real-world MCH and FP settings will become increasingly important for supporting prevention-effective adherence.

PrEP demonstration projects have generally observed higher adherence than adherence observed in the original PrEP randomized trials [8]. The data on PrEP adherence for women in demonstration projects are still limited, but women's adherence in the placebo-controlled trials of PrEP was often very low. Thus, our finding of a high TFV-DP detection frequency is encouraging for PrEP implementation for women in Africa, but should be interpreted with caution. Importantly, no protective DBS threshold has been established among cisgender women, and some evidence suggests that US-derived thresholds [9] may not be appropriate for African populations, pregnant women, or individuals with anemia. Thus, applying such thresholds to our TFV-DP concentration findings needs cautious interpretation.

We found that women with partners known to be living with HIV and those with who recently experienced sexual violence were more likely to have detectable TFV-DP. This finding suggests that women who are aware of their high HIV risk may be self-motivated to use PrEP in programmatic settings. In our evaluation, women <24 years old were less likely to have detectable TFV-DP. Qualitative studies have found that adolescent girls and young women frequently interrupt PrEP pill-taking during periods of low risk perception (e.g., while their male partner is away) [10]. Messaging on PrEP tailored to life events common among adolescent girls and young women is needed to strengthen appropriate PrEP use in this group.

We also found less frequent TFV-DP detection among pregnant women, compared to nonpregnant women. Common symptoms of pregnancy overlap with PrEP-related side effects experienced during early PrEP use, such as nausea, which negatively impacts adherence among pregnant women [11]. Compared to nonpregnant women, pregnant women more frequently report side effects as a reason for discontinuing PrEP [4]. It is important to develop PrEP adherence strategies for pregnant women that address issues unique to pregnancy, such as mitigating side effects. Additionally, pregnancy may alter the pharmacokinetics of oral PrEP among women living without HIV, which could contribute to the lower TFV-DP concentrations that we observed among pregnant women [12].

We intentionally evaluated a routine delivery setting to investigate PrEP adherence in a real-world context. However, this meant relying on programmatic data that had limited variables beyond PrEP outcomes and on screening information mainly captured via self-reports. Studies are needed that evaluate what motivates PrEP adherence within MCH/FP settings and that test strategies to improve PrEP adherence in this unique context. We restricted TFV-DP quantification to DBS samples from women who reported swallowing PrEP pills in the last 14 days, and found that those with behavioral risk factors for HIV more frequently had detectable TFV-DP. Future evaluations could incorporate other biomarkers of longer-term PrEP exposure, such as hair TFV levels, which estimate cumulative exposure over months and are not altered during pregnancy [13].

CONCLUSIONS

We frequently detected TFV-DP among blood samples collected in a programmatic evaluation of PrEP delivery to Kenyan women within routine MCH and FP clinics. Our results suggest that African women receiving PrEP programmatically who report persistent daily use of PrEP in the first month have evidence of drug exposure.

Notes

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