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Differences in Cumulative Exposure and Adherence to Tenofovir in the VOICE, iPrEx OLE, and PrEP Demo Studies as Determined via Hair Concentrations

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Abstract

Pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) prevented HIV acquisition among men and women in several trials and is broadly recommended. In the VOICE and FEM-PrEP trials, however, TDF/FTC-based PrEP did not prevent HIV acquisition among women in eastern and southern Africa. Tenofovir was detected in plasma, reflecting exposure and adherence in recent days, in fewer than one-third of participants. Drug concentrations in hair, which represent cumulative exposure and adherence over weeks to months, have never previously been examined among women on PrEP. We compared tenofovir hair concentrations among women assigned to oral TDF/FTC in the VOICE trial to those among men and transgender women enrolled in 2 open-label PrEP studies, the iPrEx open-label extension (OLE) study and the U.S. PrEP Demonstration Project (PrEP Demo). Tenofovir hair concentrations were detectable in 55% of person-visits in VOICE, 75% of person-visits in iPrEx OLE ($p = .006$), and 98% of person-visits in PrEP Demo ($p < .001$). Median tenofovir hair concentrations corresponded to an estimated 0.2, 2.9, and 6.0 TDF/FTC doses taken per week in the three studies, respectively. In VOICE, combining tenofovir concentration data from plasma and hair suggested inconsistent, low-level product use. Incorporation of both short- and long-term adherence measures may allow for an improved understanding of patterns of drug-taking among women during global PrEP roll-out.

Keywords: pre-exposure prophylaxis, adherence monitoring, HIV prevention, HIV and women, hair concentrations, plasma concentrations

Introduction

Tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-based pre-exposure prophylaxis (PrEP) was effective in preventing HIV acquisition among men and women in several trials[1–4] and is now recommended by the World Health Organization[5] and the Centers for Disease Control and Prevention[6] for individuals at substantial risk of HIV acquisition. However, TDF/FTC-based PrEP did not reduce HIV incidence in the VOICE (MTN-003)[7] and FEM-PrEP[8] trials, which both enrolled predominantly young, sexually active African women. These findings have been largely attributed to poor adherence to study product (based on detection of drug in plasma) in both placebo-controlled trials, despite high rates of self-reported adherence.[9] Moreover, given lower tenofovir (TFV) concentrations in cervicovaginal tissue compared to

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rectal tissue,[10,11] pharmacokinetic modeling data suggest that women may need to be highly adherent to daily TDF/FTC-based PrEP for protection against vaginal exposure.[12]

Prior analyses in VOICE demonstrated limited drug exposure in days preceding quarterly study visits based on TFV concentrations in plasma.[7,13] However, few studies have examined longer term drug exposure among women on PrEP or compared short- and long-term pharmacologic measures of exposure. Drug concentrations in hair reflect cumulative exposure and can estimate adherence over weeks to months.[14] For example, drug concentrations in the 1.5 cm of hair closest to the scalp represent exposure over approximately six preceding weeks. Low but detectable drug levels in hair will indicate intermittent use that may not be ascertained by monthly or quarterly analyses of TFV levels in plasma. Although concentrations of drug in plasma and hair cannot individually delineate week-to-week variations in use, combining these two measures can help to estimate patterns of drug-taking by providing information on both short- and long-term use. Hair concentrations of TFV are linearly related to TDF dose,[15] and correlate strongly with concentrations of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS).[16]

In this study, using samples from VOICE, we examine hair concentrations of TFV among women on PrEP for the first time. We further compare these hair concentrations to drug levels in plasma among VOICE participants, as well as to hair concentrations of TFV in men and transgender women enrolled in two large, open-label PrEP studies.

Materials and Methods

Study population and sample collection

The MTN-003 (VOICE) study (NCT00705679), a phase IIb, double-blinded, randomized placebo-controlled trial in the Microbicide Trials Network (MTN), was conducted from December 2009 through August 2012 and enrolled HIV-uninfected women in South Africa, Uganda, and Zimbabwe.[7] Plasma samples were collected at quarterly visits, and hair samples were collected from a subset of participants by cutting $\sim$100 strands of hair from the occipital portion of the scalp. This analysis only includes participants assigned to the active oral TDF/FTC study arm.

Hair samples, but not plasma samples, were also collected in two open-label PrEP studies that enrolled men and transgender women: the iPrEx open-label extension (OLE) study[16,17] and the U.S. PrEP Demonstration Project (PrEP Demo).[18] For all three studies, hair was stored at ambient temperature and shipped to the University of California, San Francisco hair analytical laboratory for analysis. All study participants provided written informed consent for the parent study, with opt-in for hair collection, and ethics approval was obtained from participating institutions.

Measurements

Self-reported adherence was measured in the VOICE study based on recall over the 7 days before the study visit closest to the hair collection visit. Concentrations of TFV in hair were measured via liquid chromatography/tandem mass spectrometry (LC/MS-MS) using a validated assay[15] approved by the National Institute of Allergy and Infectious Diseases (NIAID) Division of Acquired Immunodeficiency Syndrome (DAIDS)-supported Clinical Pharmacology and Quality Assurance (CPQA) Program.

The proximal section of the thatch of hair is cut into to 1–2 mm length segments and 5 mg is weighed and processed. Hair samples were analyzed for tenofovir using a Shimadzu LC-20AD HPLC system coupled to a Micromass Quattro Ultima triple quadrupole mass spectrometer using electrospray positive ionization. Single reaction monitoring analyses for the mass transitions MH^+ *m/z* 288 to *m/z* 176 (tenofovir) and MH^+ *m/z* 294 to *m/z* 182 (tenofovir-d6 [internal standard]) was performed on a reverse-phase column (Synergi POLAR-RP, 4 μm, 4.6 $\times$ 150 mm) and a gradient system of aqueous to 45% methanol both containing ammonium acetate (5 mM), 0.06% trifluoroacetic acid, and 3 mg/L ammonium phosphate at a flow rate of 1 ml/min for 6 min. Sample preparation consisted of the incubation of hair samples ($\sim$5 mg) in a 50% aqueous methanol solution containing 1% trifluoroacetic acid, 0.5% hydrazine, and tenofovir-d6 at 37°C overnight (>12 h) in a shaking water bath. Following centrifugation, the supernatant was then evaporated and injected for analysis by LC-MS/MS.

The CPQA-approved assay has been validated from 2 to 400 pg TFV/mg hair and long-term studies show stability of TFV hair concentrations in hair over years of storage. For each study, TFV concentrations in the 1.5 cm of hair closest to the scalp, representing exposure over $\sim$6 weeks, were measured. Plasma TFV concentrations were measured using an ultraperformance LC/MS-MS method with a lower limit of quantification of 0.31 ng/ml, as previously described.[7]

Statistical analysis

Spearman correlation coefficients were used to compare TFV hair and plasma concentrations to self-reported adherence. We also examined the concordance of TFV detection in hair and plasma in VOICE (if plasma was collected within 1 month of hair sampling). Median TFV hair concentrations and the proportion of hair samples with detectable TFV concentrations in the VOICE hair substudy were compared to those in the iPrEx OLE and PrEP Demo hair substudies.

The number of doses of TDF/FTC taken per week in each study was estimated by comparing hair concentration measurements in the VOICE, iPrEx OLE, and PrEP Demo to those in the STRAND study.[15] The STRAND study enrolled HIV-noninfected volunteers who received 2, 4, or 7 directly observed doses of TDF per week with subsequent collection of hair and determination of dose–concentration relationships.[15] A regression equation was fit to the number of doses and TFV hair concentrations; in previous analyses, hair concentrations of TFV were found to be log linear to the number of doses per week.[15] We fit this relationship and used the parameter estimates to solve for the expected number of doses per week associated with any TFV hair concentration, as previously described.[19] This formula was then applied to the observed hair concentration measurements in the VOICE, iPrEx OLE, and PrEP Demo.

P-values for comparing hair concentrations and rates of detectability between the studies were obtained from generalized estimating equation models using empirical standard errors (SAS version 9.4 GENMOD procedure, SAS Institute, Cary, NC).

Table 1. Characteristics of Participants in the VOICE, iPrEx OLE, and PrEP Demo Hair Substudies

	VOICE (N = *47*)	*iPrEx OLE* (N = *220*)	*PrEP Demo* (N = *280*)
Person-visits	47	838	875
Gender, *n* (%)			
Cisgender female	47 (100%)	0	0
Transgender female	0	20 (9.1%)	3 (1.1%)
Male	0	200 (90.9%)	276 (98.6%)
Other	0	0	1 (0.4%)
Age, years, median (range)	27 (19–34)	29 (19–70)	34 (19–65)
Country, *n* (%)			
Brazil	—	52 (23.6)	—
Ecuador	—	26 (11.8)	—
Peru	—	86 (39.1)	—
South Africa	18 (38.2)	8 (3.6)	—
Thailand	—	12 (5.5)	—
Uganda	10 (21.3)	—	—
United States	—	25 (11.4)	280 (100)
Zimbabwe	19 (40.4)	—	—
Weight, kg, mean (SD)	66.6 (15.9)	72 (17)	81.4 (16.1)
eGFR, ml/min, median (IQR)	129 (125–155)	111 (96–126)	97.7 (87.1–111.1)
Weeks on study at time of hair collection, median (IQR)	55 (52–60)	40 (24–60)	24 (12–36)

eGFR, estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range; PrEP, pre-exposure prophylaxis; OLE, open-label extension.

Results

Participants in hair substudies of VOICE, iPrEx OLE, and PrEP Demo

Among 47 women who participated in the VOICE hair substudy, the median age was 27 years (range 19–34) and 55% were married; all were from sub-Saharan African countries (Table 1). Predominantly male participants and a smaller number of transgender female participants were enrolled in the iPrEx OLE ($N = 220$) and PrEP Demo ($N = 280$) hair substudies. Median duration of follow-up was at least 24 weeks at the time of hair collection in all three studies: 55 weeks in VOICE (interquartile range [IQR] 52–60, range 47–107), 40 weeks in iPrEx OLE (IQR 24–60, range 11–84), and 24 weeks in PrEP Demo (IQR 12–36, range 12–48).

Concordance of hair and plasma detection, and correlation between hair concentrations and self-reported adherence in VOICE

Of 22 VOICE participants with paired hair and plasma samples, TFV was detected in 19.2% of plasma and 54.5% of hair samples. Self-reported adherence and TFV hair concentrations were poorly correlated ($r = 0.10$, 95% confidence interval [CI] −0.21 to 0.39, $p = .53$), as were self-reported adherence and TFV plasma concentrations ($r = 0.20$, 95% CI −0.16 to 0.52, $p = .26$). One VOICE participant in this substudy acquired HIV infection; TFV hair and plasma concentrations were not detectable at her seroconversion visit.

Tenofovir detection and estimated doses taken in VOICE, iPrEx OLE, and PrEP Demo

Hair concentrations of TFV were detected among 55.3% of 47 person-visits in VOICE, compared to 75.4% of 838 person-visits in the iPrEx OLE study ($p = .006$) and 97.6% of 875 person-visits in PrEP Demo ($p < .001$), (Table 2). Median TFV hair concentrations were 2.4 pg/mg (IQR below the limit of quantitation [BLQ] to 16.8) in VOICE, 17.1 pg/mg (IQR 2.2–35.2) in iPrEx OLE ($p < .001$), and 34.5 pg/mg (IQR 26.1–44.4) in PrEP Demo ($p < .001$), corresponding to an estimated 0.2, 2.9, and 6.0 TDF doses taken per week in the three studies, respectively. Among the 26 VOICE participants with detectable hair concentrations of TFV, the

Table 2. Detection of Tenofovir Hair Concentrations, Estimated Doses of TDF/FTC-Based PrEP Taken per Week, and HIV Incidence in the VOICE, iPrEx OLE, and PrEP Demo Studies

Study	*% TFV detected in hair*	*TFV hair concentration, pg/mg, median (IQR)*	*Estimated doses of TDF/FTC taken per week*	*HIV-1 incidence per 100 py on TDF/FTC (95% CI)*[a]	*Hazard ratio for HIV-1 infection (95% CI)*[a,b]
VOICE	55.3	2.4 (BLQ-16.8)	0.2	4.7 (3.6–6.1)	1.04 (0.73–1.49)
iPrEx OLE	75.4	17.1 (2.2–35.2)	2.9	1.8 (1.3–2.6)	0.51 (0.26–1.01)
PrEP Demo	97.6	34.5 (26.1–44.4)	6.0	0.43 (0.05–1.5)	N/A

[a]In parent study population.
[b]Hazard ratio for HIV-1 infection in TDF/FTC arm compared to placebo arm in parent study.
BLQ, below the limit of quantitation; py, person-years; TFV, tenofovir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; CI, confidence interval.

median hair concentration was 7.2 pg/mg (IQR 3.1–33.3), corresponding to an estimated 1.1 TDF doses taken per week. The median TFV hair concentration at the last study visit at which hair was collected was 14.4 pg/mg (IQR BLQ to 36.2) in iPrEx OLE (72 weeks) and 33.9 (IQR 25.7–44.2) in PrEP Demo (48 weeks).

The observed incidence of HIV infection in the full study population of VOICE was 4.7 (95% CI 3.6–6.1) per 100 person-years among those in the TDF/FTC arm, compared to 1.8 (95% CI 1.3–2.6) in iPrEx OLE and 0.43 (95% CI 0.05–1.5) in PrEP Demo.

Discussion

Our study demonstrates that cumulative TFV exposure based on hair concentrations and rates of TFV detection was far lower among female participants in the VOICE trial than among male and transgender female participants in the iPrEx OLE and PrEP Demo studies. Whereas self-reported adherence was high, the median estimated number of doses of TDF/FTC taken per week based on hair concentrations was fewer than one in the VOICE trial. In contrast, PrEP Demo participants in the hair substudy had evidence of nearly daily use of PrEP, on average. Of note, VOICE participants received study product in a placebo-controlled trial, while in the iPrEx OLE and PrEP Demo studies, participants were all on active product and were aware that oral PrEP had been demonstrated to be an effective chemoprophylaxis strategy.

Over half of VOICE participants had detectable TFV concentrations in hair, whereas fewer than one-quarter had detectable TFV levels in plasma. Although these measures indicate long-term nonuse of study product in a substantial proportion of participants, our results also suggest that many women took study product at least once weekly in the preceding 4–6 weeks. While TFV detection in plasma, which reflects dosing in recent days, would be expected to be higher in the case of ''white coat adherence''[20] before study visits, higher rates of TFV detection in hair than in plasma in VOICE suggest more complex patterns of nonadherence. These data are consistent with the VOICE-D study, in which VOICE trial participants were retrospectively interviewed and provided with their plasma TFV results. A number of VOICE-D participants with undetectable or low plasma TFV levels reported taking study drug intermittently or not as directed, rather than not taking it at all.[21]

To our knowledge, this VOICE hair substudy is among the first to examine cumulative drug exposure/adherence in women on PrEP. The FEM-PrEP trial examined concentrations of intracellular TFV-DP in upper layer packed cells as a marker of longer term exposure, as intracellular TFV-DP has a longer half-life than TFV in plasma.[22] The Partners PrEP trial used plasma TFV concentrations above 40 ng/ml as an indicator of steady-state daily dosing, but did not incorporate a longer term measure of exposure, such as drug levels in peripheral blood mononuclear cells, DBS, or hair.[23]

Given the limitations of self-reported adherence, incorporating measures of both short-term (e.g., TFV in plasma) and longer term (e.g., TFV in hair, TFV-DP in DBS) drug exposures may allow patterns of adherence and their association with outcomes to be examined in future studies.[24] Hair collection for exposure monitoring has some feasibility advantages, particularly in resource-limited settings. For example, hair collection does not require phlebotomy, potentially reducing the number of blood draws during PrEP follow-up visits. In contrast to plasma and DBS, hair samples can be stored and shipped at ambient temperatures without biohazardous precautions, obviating the need for maintaining a cold chain and allowing shipment by regular mail.

Median TFV concentrations in hair were far lower among women in VOICE than among men and transgender women in iPrEx OLE and PrEP Demo. This discrepancy is likely explained by differential levels of adherence among women in VOICE compared to men and transgender women in the open-label studies. Data on long-term TFV exposure among women in PrEP demonstration projects and real-world settings are currently limited. Pharmacokinetic modeling data suggest that higher levels of adherence to daily TDF/FTC-based PrEP may be required for protection from vaginal compared to rectal HIV exposure.[12] Concentration thresholds for TFV in various biomatrices that correlate with protection from HIV infection have been estimated for MSM based on pharmacokinetic modeling, in conjunction with incidence data.[17,25] Similar data to allow for analogous modeling studies in women have not been available in PrEP studies to date, but are urgently needed.

There are several limitations to our study. Hair collection in VOICE occurred near the end of the trial and participation in the hair substudy was not offered to all participants; thus, only a limited number of hair samples were available for analysis. Hair was collected in an opt-in manner in all three substudies. Because hair was collected at a later median time on study in VOICE (Table 1), waning adherence over time could have contributed to differences in drug concentrations, although the median TFV hair concentrations across all visits of iPrEx OLE and PrEP Demo were similar to those at the last hair collection visit for each study.

Rates of drug-taking may also have differed in the context of the placebo-controlled VOICE study compared to the open-label studies. Because hair was not collected in other placebo-controlled PrEP trials, we were unable to compare TFV hair concentrations between men and women receiving study drug under placebo-controlled conditions. Finally, characteristics other than sex and trial stage also differed between studies and could have further contributed to differences in hair concentrations.

Using data from the VOICE hair substudy, we examine cumulative drug exposure and adherence to PrEP based on TFV hair concentrations in women for the first time. Differential results in drug detection in plasma and hair samples indicate the utility of incorporating both short- and long-term measures of adherence in future PrEP evaluations to understand patterns of drug-taking in open-label and real-world settings during global PrEP roll-out. Given evidence of some study product use (based on hair concentrations) in over half of VOICE substudy participants, and the lack of effectiveness of TDF/FTC-based PrEP in the trial, further studies are needed to evaluate objective adherence measures among female PrEP users and to elucidate protective thresholds of drug concentrations for women on PrEP.

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