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Short-Term Adherence Marker to PrEP Predicts Future Non-Retention in a Large PrEP Demo Project: Implications for Point-of-Care Adherence Testing

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Abstract

Background: Objective adherence metrics for tenofovir (TFV) disoproxil fumarate/emtricitabine(FTC)-based PrEP were critical for interpretation of efficacy in PrEP clinical trials, and there is increasing interest in using drug levels to tailor interventions for reengagement and adherence. Point-of-care immunoassays (POC) for TFV, which examine short-term adherence, are in development. However the ability of poor short-term and long-term adherence to predict future PrEP non-retention is unknown.

Setting: Secondary data analysis of a large, prospective multi-site U.S. PrEP demonstration project

Methods: An adjusted Cox-proportional hazards model examined the relationship of dried blood spot (DBS) levels of FTC-triphosphate (FTC-TP) or TFV-diphosphate (TFV-DP), measures of short-term and long-term PrEP adherence, respectively, with future study non-retention.

Results: Overall, 294 individuals (median age 33 years) contributed drug levels within the U.S. PrEP demonstration project. By study end, 27% were lost to follow-up, 25% had at least one undetectable FTC-TP level indicating poor short-term adherence, and 29% had a drug level indicating sub-optimal long-term adherence (TFV-DP<700 fmol/punch). The strongest factor associated with future study non-retention using a binary drug-level cut-off was an undetectable DBS FTC-TP level [adjusted hazard ratio (AHR) 6.3; 95% confidence interval (CI) 3.8-10.2].

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Sub-optimal long-term adherence based on low DBS TFV-DP levels was also associated with non-retention (AHR 4.3; 95% CI 2.4-7.6).

Conclusions: Both short and long-term metrics of PrEP adherence are strongly associated with future loss to follow-up in a U.S. demonstration project study. Short-term metrics of adherence, once available at the point-of-care, could be used to direct real-time tailored retention and adherence interventions.

Keywords

Pre-exposure prophylaxis; PrEP; adherence; retention in care; persistence; dried blood spot

INTRODUCTION:

Retention in care has been called the next critical issue in pre-exposure prophylaxis (PrEP) implementation.¹ Retention in diverse real-world PrEP cohorts has not matched open-label studies, with only 38–58% of adult men who have sex with men (MSM) and transwomen remaining on PrEP at 6 months and 43–63% at 12 months across U.S.-based cohorts.^{2–8} In a study of cis-gender women on PrEP in the Bronx, only 38% remained on PrEP at 6 months.⁹ Many individuals who stop PrEP remain at risk of HIV, with one study from Los Angeles demonstrating almost a four-fold higher HIV incidence in those stopping PrEP vs. those who remained on PrEP.⁸ Another study in Montreal revealed an HIV incidence of 3.9 per 100 person-years after stopping PrEP, the same HIV incidence rate seen in the placebo group of the iPrEx randomized clinical trial.¹⁰

Objective metrics of adherence, such as tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS) and tenofovir (TFV) levels in hair, have proven crucial for the interpretation of PrEP studies, with self-reported adherence performing poorly.^{11,12} PrEP adherence, which was low in initial trials, has been higher in demonstration projects by objective metrics, with only 14–35% of individuals demonstrating sub-optimal adherence (<4 doses per week estimated by TFV-DP levels in DBS <700 fmol/punch)^{12,13} in two U.S.-based projects.^{5,14} However, adherence has been much lower in young MSM, particularly Latino and Black young MSM,^{14–16} with 66% of young MSM and 78% of adolescents having sub-optimal adherence by objective metrics at week 48 in two U.S.-based studies.^{17,18}

Although prior research has examined both retention and adherence on PrEP, little is known about their relationship.^{5,16,19} Demonstration projects that incorporated drug level monitoring have combined adherence and retention into a single outcome; however the predictive ability of adherence for future retention has not been evaluated.^{5,14,15,17,18} Availability of point of care (POC) PrEP adherence testing using immunoassays is on the horizon, to be implemented as a rapid strip test analogous to a urine pregnancy test, allowing for real-time PrEP adherence feedback on dosing over the last 4 days to patients and providers.^{14,20} Emtricitabine-triphosphate (FTC-TP) in dried blood spots similarly identifies recent adherence over the previous 2–4 days,²¹ and has been collected in prior demonstration projects. If patients first develop poor adherence prior to disengaging in PrEP care, a POC urine test could be useful to target adherence interventions towards those at highest risk of stopping PrEP in the future. Knowledge of the predictive ability of adherence

metrics for future PrEP outcomes in real-world studies is needed prior to broad implementation of these tests.

The objective of our study was to examine the ability of both short and long-term adherence metrics to serve as early proxies of future non-retention in PrEP care.

Methods:

Participants included in this Analysis

The U.S. PrEP Demo Project provided TDF/FTC-based PrEP to 557 participants across study sites in 3 cities (Miami, San Francisco, and Washington D.C.) from October 2012 to February 2015. DBS were collected for the analysis of TFV-DP concentrations as a metric of long-term, average PrEP adherence over the previous 4–6 weeks, and for the analysis of emtricitabine-triphosphate (FTC-TP) concentrations as a metric of short-term adherence, reflecting a dose in the last 2–4 days.²¹ All participants consented to drug-level testing, but it was analyzed in all African-American MSM and transgender women participants, given that few individuals were recruited in these key populations,⁵ and in a random sample of remaining participants at week 4, 12, and then every 12 weeks until week 48 (n=294 total). Only individuals who attended at least one follow-up visit to provide DBS samples were included in the analysis. Participants were reimbursed \$25 for each visit attended. The study and procedures of the U.S. PrEP Demo Project have been published previously⁵ and the protocol was approved by the institutional review board at each site; procedures were followed in accordance with the Declaration of Helsinki.

PrEP drug level measurement in DBS

A quantifiable FTC-TP level served as the primary adherence metric in this analysis, representing a dose in the last 2–4 days, due to its similar assessment of recent adherence when compared to urine TFV detectability, which assess dosing within the previous 96 hours.²² For this substudy, FTC-TP levels in DBS were categorized as quantifiable vs. below the limit of quantification (BLQ) (FTC-TP <0.1 pmol/sample). To examine longer-term PrEP adherence, we used validated dosing cut-offs for TFV-DP levels in DBS to categorize participants into 5 estimated weekly pill-taking categories on average: daily drug-taking (>1250 TFV-DP fmol/punch), 4–6x weekly (700–1250 fmol/punch), 2–3x weekly (350–700 fmol/punch), <2x weekly (>BLQ-350 fmol/punch), and BLQ (<25 fmol/sample).^{12,13} We categorized sub-optimal pill-taking as <700 fmol/punch.^{12,13}

Primary Outcome

Study non-retention/loss to follow-up in this analysis was defined as attending at least one follow-up visit after enrollment, and then not returning for a clinical visit at any point. Participants with missed follow-up visits who eventually returned were counted as retained. Participants who were lost to follow-up after the enrollment visit were excluded since no DBS samples were collected.

Statistical Analysis

We performed Cox-proportional hazards models examining time to non-retention as the primary outcome. The primary predictor was DBS FTC-TP levels examined as a cut-off (BLQ vs. quantifiable) at the week 4, 12, 24, 36 visits as a time-dependent predictor. In additional models, we substituted a DBS TFV-DP cut-off indicating sub-optimal dosing (700 fmol/punch). Finally, we examined the impact of examining FTC-TP or TFV-DP levels at only the initial (week 4) follow-up visit. We tested for violations of the proportional hazards assumption by examining correlation between time and scaled Schoenfeld residuals. In multivariable models, we adjusted for age per ten years, gender identity, race/ethnicity, and study site.

Results:

Overall, 294 individuals had DBS samples analyzed within the U.S. PrEP Demo Project over 503 person-years of follow-up. Young MSM, age<25, comprised 20% of the sample, 13% were Black, 32% were Latino, and 3% identified as transwomen (Table). By study end, over a quarter of individuals in the sub-analysis (27%, N=79) were lost to follow-up after a median of 24 weeks, with a crude rate of 0.3 study discontinuations per 1 person-year; and 9% of the sample (n=26) had a missed follow-up visit. Overall, 75% of non-retained individuals reported at least 2 condomless anal sex partners at their last visit compared to 83% of retained individuals at the final, week 48 visit (p=0.09).

One-quarter (25%) of this sample had at least one BLQ DBS FTC-TP level, representing poor short-term adherence. When measuring TFV-DP in DBS, 29% of individuals had at least one drug level indicating sub-optimal long-term adherence (TFV-DP<700 fmol/punch). In unadjusted analyses, Latino ethnicity vs. White race [Hazard Ratio (HR) 1.78 95% Confidence Interval (CI):1.21–2.63; p=0.003], being at the Miami vs. San Francisco site (HR 2.37 95% CI:1.63–3.45; p<0.001), and having a BLQ FTC-TP level (HR 7.53 95% CI: 4.81–11.78; p<0.001) or suboptimal TFV-DP level (HR 4.21; 95% CI:2.57–6.90; p<0.001) were associated with a higher hazard of non-retention, while older age per ten years was inversely associated with non-retention (HR 0.79 95% CI:0.66–0.96; p=0.02) (Table). The p-value for the relationship of missing a study follow-up visit with future non-retention was 0.08 (HR 1.86; 95% CI: 0.94–3.71). In the two adjusted analyses, only BLQ FTC-TP or sub-optimal TFV-DP respectively predicted non-retention. The factor with the strongest association with future non-retention was the short-term marker of adherence: BLQ DBS FTC-TP levels [AHR 6.27; 95% CI:3.83–10.22; p<0.001]. A majority (51%) of individuals eventually lost to follow-up had a prior BLQ FTC-TP over the course of the study. Sub-optimal adherence based on DBS TFV-DP levels consistent with <4 doses per week dosing collected at every visit was also associated with non-retention (AHR 4.31; 95% CI:2.43–7.62; p<0.001), and sub-optimal DBS TFV-DP levels detected a similar number of individuals eventually lost to follow-up (47%) (Table). Using an alternate TFV-DP cut-off of very low adherence consistent with <2 doses per week (<350 fmol/punch) had minimal impact on the association with non-retention (AHR 3.92; 95% CI:2.16–7.14; p<0.001), but only identified 22% of individuals eventually lost to follow-up. In a model using all strata of estimated weekly adherence patterns based on DBS TFV-DP levels, there was a monotonic

relationship between decreasing strata of DBS TFV-DP levels and higher hazard of non-retention ($p < 0.001$).

When examining the short-term adherence measure at the week 4 visit instead of at every visit, BLQ FTC-TP remained the only factor associated with non-retention (AHR 3.05; 95% CI: 1.75–7.31; $p < 0.001$). Overall, 23% of individuals who were eventually lost to follow-up had a BLQ FTC-TP at the week 4 visit. When measuring TFV-DP levels at week 4, sub-optimal adherence remained the only factor associated with loss to follow-up (AHR 2.40; 95% CI: 1.40–4.10; $p = 0.001$); 32% of participants eventually lost to follow-up had sub-optimal adherence as measured by TFV-DP levels at week 4 (Figure).

DISCUSSION:

In a large multi-site PrEP demonstration project, a short-term objective adherence metric had the strongest association with future loss to follow-up. Although Latino ethnicity, younger age, and the Miami site were predictors of non-retention in unadjusted analysis, only objective adherence metrics predicted retention in adjusted analyses. Three-fourths of participants lost to follow-up reported having condomless receptive anal sex with at least 2 partners at their last visit, indicating potential ongoing HIV risk.

Although some patients may discontinue PrEP due to decreased HIV risk, many stop PrEP for other reasons, including difficulty attending in-person visits and receiving laboratory monitoring, concerns about taking a daily pill, toxicity, or side effects.^{23,24} A prior demonstration project in Los Angeles showed success of plasma TFV drug level feedback in motivating later PrEP adherence in spite of a 1–3 week turnaround time.¹⁴ Metrics of adherence based on PrEP drug-levels including short-term metrics, particularly if readily available as a POC test, could permit tailored PrEP re-engagement interventions in real-time.

Re-engagement and adherence interventions tailored to PrEP drug level results were acceptable to patients in initial studies examining this approach,^{25–27} and can improve future adherence.¹⁴ A POC TFV urine test, which reflects short-term adherence, can be implemented outside of research settings at the time of a routine clinic visit, with results available in < 5 minutes.^{20,28} Our analysis of data from a large, multi-site, U.S. demonstration project suggests that a short-term metric of adherence strongly predicts future poor PrEP retention in care in diverse patient populations. A recent analysis in people living with HIV found that FTC-TP, even when adjusting for TFV-DP, predicts viral suppression.²⁹ It is possible that FTC-TP, as a short-term adherence metric, may be more sensitive to changes in adherence than TFV-DP, a long-term/cumulative metric. Therefore, a real-time short-term PrEP adherence metric may be useful to trigger retention and adherence interventions in PrEP clinics. For instance, some patients struggling with adherence may need two-way, automated text message reminders; some may prefer switching to intermittent pill-taking regimens to address pill fatigue; while others may need their PrEP care integrated with substance use treatment, transgender care, or case management.^{23,30,31}

Limitations of this analysis include a smaller sample size, with few African-Americans and transwomen recruited into the study. It is unknown what impact knowledge that real-time

feedback will be provided at the clinical visit will have on patient behavior at future visits, such as increasing adherence just prior to visits (e.g. “white coat adherence”).²⁸ A combination of short-term and long-term metrics of adherence, such as TFV levels in urine (short-term) and DBS TFV-DP levels or TFV levels in hair (both long-term), may better tease out intermittent vs. sustained adherence patterns.¹¹ The magnitude of study non-retention in U.S. PrEP Demo may have been impacted by patients having less incentive to attend the week 48 visit given that future study drug would not be available. In addition, demonstration project non-retention may not accurately reflect non-retention in care in a real-world setting, and patients in real-world settings may be less likely to attend clinic visits if they are not adherent to PrEP, compared with those in a study who were reimbursed \$25 for study visits. Finally, we were unable to assess what proportion of individuals who were lost to follow-up remained at risk of HIV.

In conclusion, we have demonstrated a strong independent association between short and long-term adherence to PrEP and future retention. Given that PrEP retention in care is poor in real-world settings and point-of-care short-term adherence metrics to PrEP via urine-based immunoassays are imminent, this study suggests that measuring short-term adherence at the POC could identify patients at increased risk for being lost of follow-up to deliver targeted, real-time adherence feedback counseling or other evidence-based interventions.

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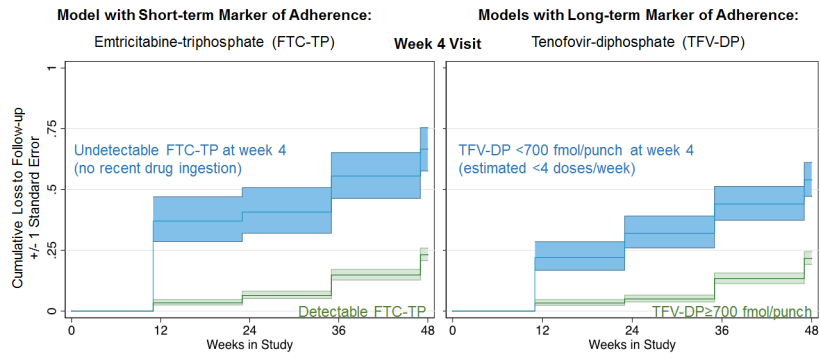


Figure:
Short and Long-Term Markers of Adherence at the Week 4 Visit Predict Loss to Follow-Up in the U.S. PrEP Demo Project

Table 1:

Characteristics of the Sample and Predictors of Non-Retention in Cox-Proportional Hazards Models

	Overall % N=294	Unadjusted HR: 95% CI	DBS FTC-TP Model AHR: 95% CI	DBS TFV-DP Model AHR: 95% CI
Age at study entry, median (IQR) ¹	33 (27-42)	0.79: 0.66-0.96 ²	0.90: 0.71-1.15 ²	0.82: 0.64-1.04 ²
Race: White	45	Ref.	Ref.	Ref.
Asian	5	1.31: 0.56-3.05	1.42: 0.52-3.87	1.91: 0.71-5.12
Black	13	1.73: 0.93-3.25	1.09: 0.49-2.44	0.89: 0.39-2.02
Latino	32	1.78: 1.21-2.63	1.29: 0.65-2.53	1.36: 0.69-2.67
Mixed/other	4	0.94: 0.34-2.60	1.62: 0.55-4.80	1.41: 0.48-4.20
Transwoman (vs. MSM)	3	1.12: 0.28-4.54	0.87: 0.20-3.67	0.99: 0.24-4.11
Site: San Francisco	36	Ref.	Ref.	Ref.
Miami	31	2.37: 1.63-3.45	1.13: 0.59-2.18	1.15: 0.59-2.23
Washington D.C.	32	0.92: 0.52-1.58	0.73: 0.38-1.40	0.78: 0.41-1.51
Sub-optimal adherence by TFV-DP (<700 fmol/punch) at any visit ³	29 ²	4.21: 2.57-6.90 ³	-	4.31: 2.43-7.62 ³
Undetectable DBS FTC-TP at any visit ³	25 ²	7.53: 4.81-11.78 ³	6.27: 3.83-10.22 ³	-

AHR: Adjusted hazard ratio; DBS: Dried Blood Spot; FTC-TP: emtricitabine-triphosphate; TFV-DP: tenofovir-diphosphate; CI: Confidence interval; IQR: inter-quartile range; MSM: Men who have sex with men.

¹ Scaled per ten years

² Lowest documented adherence during course of the demo project

³ Treated as a time-dependent covariate in survival analysis