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Predictors of Long-Term HIV Pre-exposure Prophylaxis Adherence After Study Participation in Men Who Have Sex With Men

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Background: Efficacy of HIV pre-exposure prophylaxis (PrEP) among men who have sex with men is well documented in randomized trials. After trial completion, participants are challenged with acquiring PrEP on their own and remaining adherent.

Methods: This was a follow-up study of the TAPIR randomized controlled multicenter PrEP trial. Participants were contacted after their last TAPIR visit (ie, after study-provided PrEP was discontinued) to attend observational posttrial visits 24 and 48 weeks later. Adherence during TAPIR and posttrial visits was estimated by dried blood spot intracellular tenofovir diphosphate levels (adequate adherence defined as tenofovir diphosphate levels >719 fmol/punch). Binary logistic regression analysis assessed predictors of completing posttrial visits and PrEP adherence among participants completing ≥ 1 visit.

Results: Of 395 TAPIR participants who were on PrEP as part of the TAPIR trial for a median of 597 days (range 3–757 days), 122

(31%) completed ≥ 1 posttrial visit (57% of University of California San Diego participants completed posttrial visits, whereas this was 13% or lower for other study sites). Among participants who completed ≥ 1 posttrial visit, 57% had adequate adherence posttrial. Significant predictors of adequate adherence posttrial were less problematic substance use, higher risk behavior, and adequate adherence in year 1 of TAPIR.

Conclusion: More than half of PrEP users followed after trial completion had successfully acquired PrEP and showed adequate adherence. Additional adherence monitoring and intervention measures may be needed for those with low PrEP adherence and problematic substance use during the first year of trial.

Key Words: adherence, continuum, real-life cohort, substance use, risk behavior

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INTRODUCTION

Despite declining numbers of incident infections, HIV continues to have a disproportionate impact on men who have sex with men (MSM).^{1–3} The efficacy of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) for HIV pre-exposure prophylaxis (PrEP) in MSM has been well documented in several randomized controlled trials.^{4–6} The effectiveness of TDF/FTC for HIV PrEP strongly depends on adherence.^{7,8} This was also outlined by a recently published mathematical model, showing increased adherence was the only factor that reduced the number needed to treat with PrEP to prevent one HIV infection.⁹ For MSM, the iPrEx study was pivotal in showing that TDF/FTC reduced the risk of HIV infection in MSM by >90% in those with adherence defined by tenofovir diphosphate (TFV-DP) drug levels commensurate with 4 or more tablets per week.¹⁰

PrEP adherence measures vary widely between randomized controlled trials.^{4–6,11–15} Although self-reported adherence measures seem to overestimate actual adherence,¹⁶ trials measuring TFV-DP drug levels reported adequate adherence (corresponding to 4 or more tablets a week) in about 80%–90% of study participants, whereas near-perfect adherence (corresponding to 7 or more tablets a week) in 40%–50% of study participants.^{17,18} However, these published data do not inform us about PrEP use and adherence after roll-off from PrEP trials

and PrEP demonstration projects, when participants are challenged with establishing care, acquiring PrEP, and remaining adherent.^{14,19–22}

This study aimed to identify predictors of the PrEP adherence posttrial period for participants completing the TAPIR randomized controlled trial of text messaging versus standard care for adherence to daily TDF/FTC PrEP in MSM in Southern California between 2014 and 2016 (NCT01761643).

MATERIAL AND METHODS

Setting and Participants

To achieve this goal, we leveraged the ending of an existing PrEP demonstration project, the TAPIR trial (CCTG595), a randomized controlled trial of individualized text messaging versus standard care for adherence to daily TDF/FTC PrEP, conducted between 2014 and 2016 (<http://www.clinicaltrials.gov/ct2/show/NCT01761643>).¹⁷ In TAPIR, PrEP was given in combination with safety monitoring, HIV testing, and risk reduction counseling to MSM and transgender women.¹⁷ The pool of potential participants for follow-up came from 395 patients (392 MSM and 3 transgender women) who had at least one dried blood spot (DBS) PrEP level measured during TAPIR at 4 Southern California medical centers [University of California San Diego (UCSD), University of Southern California (USC), Long Beach Health Department, and Harbor-University of California Los Angeles (UCLA)].²³ Eligible participants for TAPIR were HIV-uninfected MSM and transgender women (age ≥ 18 years) with elevated risk of HIV acquisition as previously published.²³ Although the primary outcome for TAPIR was TFV-DP drug levels measured at weeks 12 and 48, study participants were allowed to continue past week 48 on study drug until the last subject completed their week 48 visit; at that timepoint, everyone was discontinued from study-provided PrEP.¹⁷ At the final 2 visits, participants were provided with information regarding local PrEP providers and where to obtain PrEP in the community, but they were on their own to self-initiate PrEP continuation. As part of the current study, we conducted prospective strictly observational (ie, no PrEP services were provided) follow-up visits at least 24 weeks after TAPIR trial roll-off and a second follow-up visit at 24 weeks after the first follow-up visit. Follow-up visits were conducted at the UCSD, USC, and Harbor-UCLA only. Follow-up visits of TAPIR participants enrolled at the Long Beach Health Department were conducted at the Harbor-UCLA.

Measures

PrEP Continuation and Adherence

PrEP continuation was defined by participant self-report of linking to a provider and continuing to receive PrEP from a provider during post-TAPIR study visits. Adherence was estimated by DBS intracellular TFV-DP levels only for those who reported having taken any PrEP within the past 2 weeks. A concentration of >719 fmol/punch was used to estimate 4

or more tablets per week on average (ie, “adequate” adherence). This value is the unrounded lower quartile corresponding to the 700 fmol/punch level used in the iPrEx OLE study, which showed 0 of 28 seroconversions when TFV-DP was at or above 700 fmol/punch.²⁴ A concentration of >1246 fmol/punch was defined as “near-perfect” adherence, associated with taking 7 doses of TDF in the past week.^{24,25} Intracellular TFV-DP concentrations were performed at the last on-drug visit that occurred on or before the TAPIR 48-week visit, and at the 24- and 48-week posttrial visits for participants reporting PrEP continuance at the respective time points as described before.²⁵

Frequency of substance use in the past 3 months was assessed at week-48 TAPIR visit using a substance use screening questionnaire (SCID). We also evaluated stimulant substances use (including poppers, methamphetamine, cocaine, ecstasy, amphetamine, and other stimulants), non-stimulant substances use (including heroin, other opioids, eg, Vicodin, OxyContin, sedatives, antianxiety drugs, hallucinogens, dissociative drugs, and inhalants), and any substance use (including both stimulant and nonstimulant substances listed above). Problematic use was assessed at baseline using the Drug Abuse Screening Test (DAST10) and the Alcohol Use Disorders Identification Test (AUDIT), and defined as described before.²⁴

Self-reported sexual risk behavior was assessed at week 48 of the TAPIR trial via questionnaires. Sexually transmitted infection (STI) screening assessments during the first year of TAPIR included syphilis (serum rapid plasma regain and, if positive, confirmatory treponemal test), as well as nucleic acid amplification testing of both urine, pharyngeal, and rectal swabs for chlamydia and gonorrhea (Hologic Aptima). Newly diagnosed STIs were communicated to participants who were referred to their provider or a local sexually transmitted disease clinic for treatment. Incident STI was defined as having positive results of gonorrhea or chlamydia at any site or positive syphilis rapid plasma regain result during the first year of TAPIR. Sexual risk behavior and STI were summarized into the CalcR score, developed as an alternative tool to evaluate HIV risk based on patient-specific HIV transmission events.²⁶ The score has been generated from a mathematical equation that focuses on sexual transmission methods and biological factors that may increase HIV acquisition in the absence of PrEP: condomless receptive and insertive anal intercourse acts and incident sexually transmitted diseases including gonorrhea, chlamydia, syphilis, and herpes, as reported for the past month, as described before.²⁶

Statistical Analysis

All statistical analysis was conducted using SPSS 25 (SPSS, Inc., Chicago, IL). Demographics, PrEP adherence, substance use, and risk behaviors assessed at week 48 of the TAPIR trial were compared between participants who completed at least one posttrial visit versus those who did not using the Fisher exact test/ χ^2 test for categorical variables and the Student *t* test/Wilcoxon rank-sum test for continuous variables. The Wilcoxon signed-rank test was used to compare DBS levels between TAPIR week-48 and posttrial

TABLE 1. Demographic Data and Characteristics at Week 48 of the TAPIR Trial for UCSD Participants Who Did and Did Not Complete ≥ 1 Posttrial Visit, and Participants From the USC, Long Beach, and Harbor-UCLA Who Completed ≥ 1 Posttrial Visit, as Well as Participants From All Study Sites Who Completed Posttrial visit(s) and Had or Had Not Adequate PrEP Adherence

Variables: N(%) if Not Stated Otherwise	UCSD TAPIR Participants Who Completed ≥ 1 Posttrial Visit (n = 100)*	UCSD TAPIR Participants Who Did Not Complete Posttrial Visits (n = 74)*	P	USC, Long Beach, and UCLA TAPIR Participants Who Completed ≥ 1 Posttrial Visit (n = 22)*	Participants Who Completed ≥ 1 Posttrial Visit and Had Adequate PrEP Adherence (n = 70)	Participants Who Completed ≥ 1 Posttrial Visit but Were Not Linked to PrEP or Reached Not Adequate PrEP Adherence (n = 52)*	P
Gender			0.425				1.000
Male	100 (100%)	73 (99%)		22 (100%)	70 (100%)	52 (100%)	
Transgender male to female	0 (0%)	1 (1%)		0 (0%)	0 (0%)	0 (0%)	
Age, yr; mean (SD)	37 (10)	33 (9)	0.007	34 (9)	38 (10)	36 (11)	0.489
Race			0.879				0.364
White	74 (74%)	54 (73%)		16 (73%)	54 (77%)	36 (69%)	
Hispanic ethnicity	15 (15%)	27 (36%)	0.002	7 (32%)	11 (16%)	11 (21%)	0.462
Education			0.676				0.715
High school or lower	8 (8%)	10 (14%)		0 (0%)	4 (6%)	4/51 (8%)	
Some college	35 (35%)	26 (35%)		5/21 (24%)	25 (36%)	15/51 (29%)	
Bachelors degree	32 (32%)	22 (30%)		11/21 (52%)	22 (31%)	21/51 (41%)	
Postgraduate or advanced degree	25 (25%)	16 (22%)		5/21 (24%)	18 (26%)	12/51 (24%)	
Household income			0.359				0.983
<\$2000/mo	18 (18%)	20 (27%)		5/21 (24%)	13 (18%)	10/51 (20%)	
>\$2000/mo	77 (77%)	51 (69%)		11/21 (52%)	51 (73%)	38/51 (75%)	
Refused to answer	5 (5%)	3 (4%)		5/21 (24%)	6 (9%)	4/51 (8%)	
Intervention arm (ie, receiving daily text messages for PrEP adherence)	43 (43%)	45 (61%)	0.020	9 (41%)	29 (41%)	23 (44%)	0.757
Duration on TAPIR PrEP trial (d); mean, SD	608 (141)	462 (232)	<0.001	607 (115)	634 (105)	573 (164)	0.015
Calculated HIV sexual risk (CalcR) score (1 mo) at week-48 TAPIR visit; median, IQR	0.028 (0–0.107)	0.050 (0–0.143)	0.164	0.021 (0–0.073)	0.039 (0–0.128)	0.015 (0–0.073)	0.076
Adequate adherence week-48 TAPIR trial	90/97 (93%)	46/59 (78%)	0.007	17/21 (81%)	67 (96%)	40/48 (83%)	0.023
Near-perfect adherence week-48 TAPIR trial	48/97 (49%)	18/59 (31%)	0.020	8/21 (38%)	38 (54%)	18/48 (38%)	0.073
Alcohol Use Disorders Identification Test (AUDIT) week 48; median points (IQR)	5 (3–8)	5 (3–9)	0.918	4 (2–10)	5 (3–9)	5 (2–8)	0.803
Stimulant substance use week-48 TAPIR	27 (27%)	25/73 (34%)	0.305	8 (36%)	19 (27%)	16 (31%)	0.661
Nonstimulant substance use (alcohol, marijuana, and poppers excluded) week-48 TAPIR	43 (43%)	39/73 (53%)	0.175	9 (41%)	32 (46%)	20 (38%)	0.463
Popper use	39 (39%)	36/73 (49%)	0.176	12 (55%)	31 (44%)	20 (38%)	0.519

TABLE 1. (Continued) Demographic Data and Characteristics at Week 48 of the TAPIR Trial for UCSD Participants Who Did and Did Not Complete ≥1 Posttrial Visit, and Participants From the USC, Long Beach, and Harbor-UCLA Who Completed ≥1 Posttrial Visit, as Well as Participants From All Study Sites Who Completed Posttrial visit(s) and Had or Had Not Adequate PrEP Adherence

Variables: N(%) if Not Stated Otherwise	UCSD TAPIR Participants Who Completed ≥1 Posttrial Visit (n = 100)*	UCSD TAPIR Participants Who Did Not Complete Posttrial Visits (n = 74)*	P	USC, Long Beach, and UCLA TAPIR Participants Who Completed ≥1 Posttrial Visit (n = 22)*	Participants Who Completed ≥1 Posttrial Visit and Had Adequate PrEP Adherence (n = 70)	Participants Who Completed ≥1 Posttrial Visit but Were Not Linked to PrEP or Reached Not Adequate Adherence (n = 52)*	P
Drug Abuse Screening Test (DAST10) week 48; median points (IQR)	1 (1–2)	2 (1–3)	0.172	2 (1–4)	1 (1–2)	2 (1–3)	0.021

*N indicated for variables that were not available from all study participants.

visits. Univariate and multivariable binary logistic regression analyses assessed predictors of completing posttrial visits (model 1, UCSD participants only because posttrial follow-up rates were >50% at the UCSD, whereas they were below 13% at other study sites; alternative model 1 included participants from all sites but used the study site as clustering variable) and PrEP adherence among those who completed ≥1 visit (models 2, 3, 4, and 5, participants of all four study sites, model 4 and 5 used study site as clustering variable); alternative models 2 and 3 focused only on PrEP adherence among those on PrEP. Variables with a *P* value <0.2 in univariate analysis were included in the multivariable model. Variables in the final model were selected with a stepwise forward procedure. Model discrimination was assessed by the goodness-of-fit Hosmer–Lemeshow statistics. Odds ratios (ORs) and adjusted ORs (aORs) including 95% confidence intervals (CIs) were calculated, and a *P* value of <0.05 was considered statistically significant. The study was approved by the University of California, San Diego institutional review board, and written informed consent was obtained from all participants.

RESULTS

Of 395 TAPIR participants who were enrolled in TAPIR for a median of 597 days (range 3–757 days) and provided with free PrEP during study engagement, 122 (31%) completed one or both posttrial visits; 108 individuals completed the 24-week posttrial visit and 96 the 48-week posttrial visit. For the last follow-up, the total time of observation including both time in the trial and follow-up was median 1122 days (range 687–1534 days). The follow-up rate differed significantly between participating centers and was highest at the UCSD with 57% (100/174 participants). Lower participation was seen at other sites: 13% (17/127) at the USC, 6% (3/47) for Long Beach, and 4% (2/47) for the Harbor-UCLA. Further analyses on predictors of posttrial visits focused therefore on UCSD participants only (median TAPIR enrollment 616 days, range 21–734 days; 95 completed the 24-week posttrial visit and 82 the 48-week posttrial visit), whereas models on predictors of posttrial adherence included posttrial participants from all 4

study sites. Demographic data and characteristics at week 48 of the TAPIR trial for UCSD participants who did and did not complete ≥1 posttrial visit, as well as for the USC, Long Beach, and Harbor-UCLA participants who completed ≥1 posttrial visit are depicted in Table 1.

Univariate and multivariable logistic regression models for predicting ≥1 posttrial visit among TAPIR trial participants at the UCSD are shown in Table 2. Multivariable predictors of completing posttrial visits included more total days of TAPIR enrollment (ie, more total days of study-provided PrEP), adequate adherence at the week-48 TAPIR visit, and self-reported non-Hispanic ethnicity. Total days of TAPIR enrollment remained the strongest predictor in the stepwise approach, followed by non-Hispanic ethnicity. In the alternative model 1 that included study participants at all sites and used the study site as clustering variable, multivariable predictors of completing posttrial visits included non-Hispanic ethnicity (aOR 2.58; *P* < 0.001), adequate adherence at week 48 TAPIR visit (aOR 1.89; *P* < 0.001), no self-reported popper use (aOR for popper use 0.42; *P* < 0.001), total days of TAPIR enrollment (aOR 1.004 per day; *P* = 0.001), not being randomized in the intervention arm (aOR for intervention arm 0.59; *P* = 0.013), and more problematic alcohol use (aOR 1.07 per AUDIT score point; *P* = 0.035).

Among 122 participants who completed ≥1 posttrial visit (ie, 62 participants completed both visits, whereas 33 completed only one visit) at all sites, 95 (78%) indicated that they were on PrEP and had DBS levels measured. Overall, 70/95 (74%) had adequate adherence, and 32/95 (34%) near-perfect adherence at their last posttrial visit where DBS was measured (6 individuals had DBS levels measured at 24-week posttrial but not 48-week posttrial where they indicated that they were not on PrEP). Demographic data and characteristics of participants completing posttrial visits with and without adequate adherence are depicted in Table 1. The only significant predictor in univariate analysis of self-reported linkage to PrEP at the last posttrial visit was less problematic substance use (OR per DAST10 score point 0.757, 95% CI: 0.595 to 0.962; *P* = 0.023).

TABLE 2. Univariate and Multivariable Binary Logistic Regression Models for Predicting ≥ 1 Post-PrEP Trial Study Visit Among Participants at the UCSD

Model 1: Variables for Predicting Posttrial Visit (n = 174)	OR	95% CI	P	aOR	95% CI	P
	Univariate Model			Multivariable Model*		
Intervention arm (ie, receiving daily text messages for PrEP adherence)	0.486	0.264 to 0.897	0.021	—	—	n.s.
Age (per year)	1.044	1.011 to 1.079	0.009	—	—	n.s.
Non-Hispanic ethnicity	2.524	1.261 to 5.051	0.009	3.606	1.598 to 9.993	0.002
Higher education category	1.139	0.897 to 1.445	0.285	—	—	n.s.
Higher income category	1.212	1.019 to 1.443	0.030	—	—	n.s.
Duration on PrEP trial (per day)	1.004	1.002 to 1.006	<0.001	1.004	1.001 to 1.006	0.003
Adequate adherence end of PrEP trial study visit	3.634	1.357 to 9.731	0.010	3.517	1.238 to 9.993	0.018
Drug Abuse Screening Test (DAST10; per score point)	0.843	0.707 to 1.006	0.058	—	—	n.s.
Stimulant substance use	0.710	0.369 to 1.367	0.305	—	—	n.s.
Nonstimulant substance use (alcohol, marijuana, and poppers excluded)	0.658	0.358 to 1.207	0.176	Not included	—	—
Popper use	0.657	0.357 to 1.209	0.177	Not included	—	—
Alcohol Use Disorders Identification Test (AUDIT; per score point)	1.010	0.939 to 1.087	0.780	—	—	n.s.
Calculated HIV risk score (CalcR) month	0.323	0.028 to 3.673	0.362	—	—	n.s.

* $\chi^2 = 8.852$; $P = 0.355$ Hosmer–Lemeshow; forward Wald binary logistic regression.

Participants with adequate adherence at the week-48 TAPIR trial visit had also significantly higher DBS TFV-DP levels at last posttrial follow-up than those without adequate adherence [median 993 fmol/punch, interquartile range (IQR) 0–1397 vs. median 636 fmol/punch, IQR 0–758; $P = 0.030$]. The same was found for participants with near-perfect adherence at the week-48 TAPIR trial visit versus those without near-perfect adherence (median 1173 fmol/punch, IQR 0–1533 vs. median 791 fmol/punch, IQR 0–1092; $P = 0.021$).

For individual visits, among those who were on PrEP, 64/83 (77%) had adequate and 31/83 (37%) near-perfect adherence at 24-week posttrial; and 56/74 (76%) adequate and 26/74 (35%) near-perfect adherence at 48-week posttrial (Fig. 1). DBS TFV-DP levels differed significantly between week 48 of TAPIR and week 24 posttrial ($P < 0.001$; the Wilcoxon signed-rank test; Fig. 1). However, a plot of individual adherence levels shows that levels stayed above adequate adherence in most participants (Fig. 1).

Less problematic substance use at the week-48 TAPIR trial visit was the only significant predictor of reaching adequate adherence posttrial in the multivariable model of all participants with posttrial visits (Table 3). The multivariable model for near-perfect adherence indicated that near-perfect adherence at the week-48 TAPIR trial visit and higher CalcR scores at the week-48 TAPIR trial visit (indicative of higher sexual risk behavior) were significant predictors for near-perfect adherence at the last posttrial visit (Table 3). In the multivariable model 4 (ie, using the study site as clustering variable), higher CalcR scores (aOR 14.02 per score point; $P < 0.001$), less problematic substance use (aOR 0.69 per DAST10 score point; $P < 0.001$), adequate adherence during week 48 of TAPIR (aOR 4.02; $P < 0.001$) and longer enrollment into TAPIR (aOR 1.003; $P = 0.003$) remained all significant predictors of adequate adherence at

the last post-trial visit. In the multivariable model 5 (ie also using study site as clustering variable) higher CalcR scores (aOR 60.76 per score point; $P < 0.001$), longer enrollment into TAPIR (aOR 1.004 per day; $P < 0.001$), older age (aOR 1.04 per year; $P < 0.001$), and absence of popper use (aOR 0.72 for popper use; $P = 0.008$) remained all significant predictors of near-perfect adherence at the last post-trial visit.

In alternative models focusing only on those 95 participants who self-reported being on PrEP and therefore had DBS TFV-DP levels measured, adequate adherence at TAPIR week 48 was the only significant predictor of adequate adherence at the last posttrial visit. Similarly, near-perfect adherence at week 48 of TAPIR was the only predictor of near-perfect adherence at the last posttrial visit (see Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/QAI/B287>).

DISCUSSION

We followed PrEP users after completing a clinical PrEP trial to evaluate predictors of posttrial PrEP adherence in a well-characterized cohort of mostly MSM at risk of HIV acquisition. Two major findings are evident. First, adequate PrEP adherence was found frequently in those who completed ≥ 1 posttrial follow-up visit, and less problematic substance use and adequate PrEP adherence during the PrEP trial were the predictors of adequate adherence posttrial. Second, near-perfect adherence posttrial was found among those with higher sexual risk behavior and near-perfect PrEP adherence during the trial.

Overall, rates of follow-up posttrial varied widely between sites and reached 57% at the UCSD. Those who did not complete posttrial visits at the UCSD were younger, more likely randomized into the TAPIR intervention arm, had higher income, more problematic drug use, were more likely

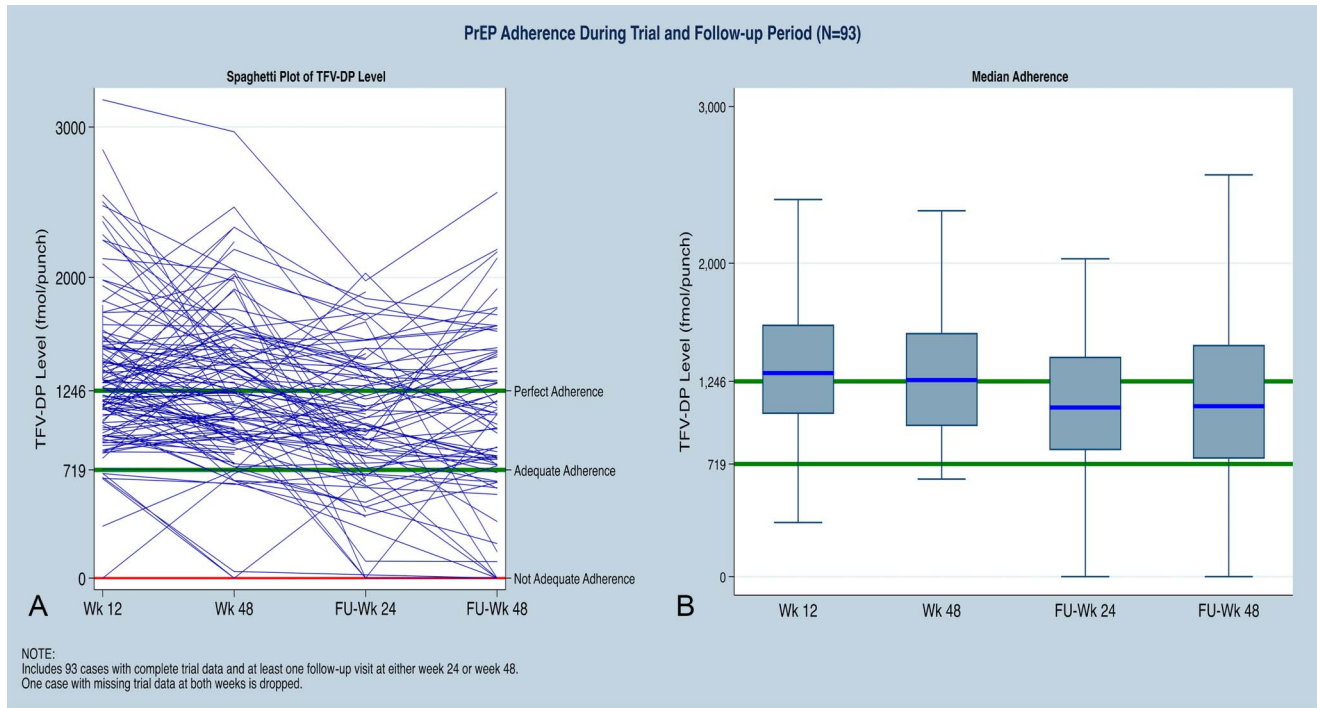


FIGURE 1. Longitudinal DBS PrEP levels during TAPIR and posttrial. The figure includes 93 individuals who had DBS levels measured during week 24 and 48 of TAPIR and also at either week 24 or week 48 of posttrial (FU) visits. A, Spaghetti Plots of PrEP levels, B) Median DBS levels at the different Timepoints.

Hispanic, shorter follow-up duration in the TAPIR trial, and had lower adherence at week 48 of TAPIR. Only the latter 3 remained significant predictors in the multivariable model. Longer total TAPIR trial participation was the most important predictor for completing posttrial visits, indicating that longer duration of follow-up and study-provided free PrEP during a trial may also increase posttrial study linkage. Although PrEP linkage and adherence could not be assessed in participants not returning for follow-up visits, it could be hypothesized that PrEP linkage may have been lower among those not returning for follow-up visits. If that is true, findings that Hispanic MSM were less likely to present for follow-up may be seen in line with previous reports. Hispanic MSM are disproportionately affected by the HIV epidemic, because of social and structural factors contributing to high-risk behaviors and limited PrEP use in real-life settings (prescribed to only ~3% of Hispanic MSM who could benefit).^{27–29} This is particularly true for Hispanic MSM younger than 25 years for which a 35% increase in new HIV diagnoses was observed in California from 2005 to 2013.^{30,31} Also, previous reports from San Diego, where the majority of TAPIR participants were enrolled, indicate that Hispanic MSM were less likely to come back for follow-up visits after 3–6 months.^{32–34}

About 60% of participants who completed posttrial visits had adequate PrEP adherence. Depending on the model, either less problematic substance use or adequate adherence during the TAPIR trial was the only significant predictors of adequate adherence posttrial in the multivariable model.

MSM with problematic substance use often face important individual barriers (eg, HIV-related stigma and

substance use) and structural barriers (eg, economic and health care) that may reduce linkage and adherence to PrEP.^{35–40} Importantly, substance use was not associated with lower PrEP adherence in the TAPIR trial.²³ However, among participants who completed posttrial visits, problematic substance was a major predictor of not reaching adequate PrEP adherence, by mostly impacting the ability of participants to successfully link to PrEP providers after the study. By contrast, adequate adherence during the TAPIR trial was the only significant predictor of adequate adherence posttrial in those who were on PrEP. Although the TAPIR text messaging intervention itself was not associated with higher adherence posttrial, this finding may nevertheless indicate that measures taken to enable participants' adherence within a trial may have far reaching effects beyond trial roll-off. Near-perfect adherence was observed in about half of those with adequate adherence posttrial and best predicted by having near-perfect adherence during the TAPIR trial. The second significant predictor of near-perfect adherence posttrial was higher sexual risk behavior, indicating that those most at risk may have insight into their HIV risk and appropriately be diligent with PrEP adherence.

There are important limitations to this study, in particular the number of participants who completed posttrial visits. Given that the proportion of participants who completed posttrial visits varied widely between study sites, we had to focus our model on predictors of posttrial visits on UCSD participants only. There are a number of factors that went into this. The UCSD may have had greater success

TABLE 3. Univariate and Multivariable Binary Logistic Regression Models for Predicting PrEP Linkage Plus Adequate (Model 2) and Near-Perfect PrEP Adherence (Model 3) at the Last Posttrial Visit Where Levels Were Measured Among Participants at All Four Participating Centers

Variables for Predicting Posttrial PrEP Adherence (n = 122)	OR	95% CI	P	aOR	95% CI	P
	Univariate Model			Multivariable Model		
Model 2: Variables for predicting adequate PrEP adherence at the last posttrial visit						
Intervention arm (ie, receiving daily text messages for PrEP adherence)	0.897	0.435 to 1.851	0.769			
Study site other than UCSD	0.768	0.304 to 1.937	0.576			
Age (per year)	1.016	0.979 to 1.053	0.401			
Non-Hispanic ethnicity	1.333	0.528 to 3.368	0.543			
Higher education category	0.959	0.716 to 1.285	0.779			
Higher income category	1.059	0.861 to 1.304	0.587			
Duration on PrEP trial (per day)	1.003	1.000 to 1.006	0.025	—	—	n.s.
Adequate adherence week-48 PrEP trial study visit	4.063	1.019 to 16.20	0.047	—	—	n.s.
Drug Abuse Screening Test (DAST10; per score point)	0.707	0.548 to 0.914	0.008	0.717	0.550 to 0.933	0.013
Stimulant substance use	0.800	0.363 to 1.759	0.578			
Nonstimulant substance use (alcohol, marijuana, and poppers excluded)	1.179	0.571 to 2.437	0.656			
Popper use	1.110	0.537 to 2.296	0.778			
Alcohol Use Disorders Identification Test (AUDIT; per score point)	0.974	0.909 to 1.043	0.447			
Calculated HIV risk score (CalcR) month	1.821	0.072 to 45.83	0.716			
Model 3: Variables for predicting near-perfect PrEP adherence at the last posttrial visit*						
Intervention arm (ie, receiving daily text messages for PrEP adherence)	1.427	0.654 to 3.316	0.351			
Study site other than UCSD	1.053	0.372 to 2.978	0.923			
Age (per year)	1.039	0.998 to 1.082	0.060	—	—	n.s.
Hispanic ethnicity	0.963	0.340 to 2.724	0.943			
Higher education category	0.854	0.609 to 1.198	0.361			
Higher income category	1.133	0.888 to 1.446	0.316			
Duration on PrEP trial (per day)	1.004	1.000 to 1.008	0.073	—	—	n.s.
Near-perfect adherence week-48 PrEP trial study visit	6.221	2.412 to 16.04	<0.001	5.711	2.160 to 15.10	<0.001
Drug Abuse Screening Test (DAST10; per score point)	0.830	0.622 to 1.108	0.206			
Stimulant substance use	0.765	0.305 to 1.919	0.569			
Nonstimulant substance use (alcohol, marijuana, and poppers excluded)	0.877	0.386 to 1.992	0.754			
Popper use	0.769	0.336 to 1.763	0.535			
Alcohol Use Disorders Identification Test (AUDIT; per score point)	0.976	0.898 to 1.061	0.569			
Calculated HIV risk score (CalcR) month	21.283	0.708 to 639.5	0.078	98.444	1.261 to 7687	0.039

*Multivariable model: $\chi^2 = 7.780$; $P = 0.255$ Hosmer–Lemeshow; forward Wald binary logistic regression.

with efforts to keep subjects engaged in follow-up. The study site may also have been more convenient and less challenging to complete poststudy visits. It is possible that many individuals who did not attend poststudy visits may not have continued PrEP after the study ended and therefore not interested in follow-up. Multiple attempts were made to call individuals, but many did not respond or did not give reason for nonparticipation. Also, there are important limitations to note regarding our setting, where all study sites were located in one geographic area, and

a subset of participants were already known to have higher adherence from the TAPIR study, making our setting different from other real-world settings. Finally, PrEP continuation and linkage was defined by participant self-report only, making this a less reliable outcome and preventing our study from detailed assessments of predictors of PrEP linkage.

In conclusion, PrEP users followed up for up to 4 years had high rates of adequate adherence, suggesting that PrEP can be used effectively by individuals for years.

Follow-up posttrial was predicted by longer trial enrollment, higher PrEP adherence during the trial, and non-Hispanic ethnicity. Longer-term adequate adherence was best predicted by having adequate adherence during the PrEP trial and less problematic substance use. Additional adherence monitoring and intervention measures may therefore be needed for those with low PrEP adherence during the first year and those with problematic substance use.

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