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# Trajectories and Predictors of Longitudinal Preexposure Prophylaxis Adherence Among Men Who Have Sex With Men

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***Background.*** Adherence is necessary for efficacy of preexposure prophylaxis (PrEP), and text-messaging methods are promising tools for both adherence assessment and support. Although PrEP adherence is variable, little research has examined patterns of variability or factors associated with longitudinal use.

***Methods.*** In the context of a randomized controlled trial of text-messaging versus standard of care for PrEP adherence, 181 men who have sex with men received once-daily tenofovir disoproxil fumarate/emtricitabine and daily adherence texts for 48 weeks. Growth mixture modeling (GMM) was used to identify subgroups of individuals with similar trajectories of text-reported adherence. Between-group differences in pharmacologic measures of adherence (ie, tenofovir diphosphate and emtricitabine triphosphate levels), as well as predictors and study-end attitudes associated with group membership, were examined.

***Results.*** GMM identified 4 trajectories of text-reported adherence. Classes with higher text-reported adherence had higher drug concentrations. Younger age and minority race were associated with lower adherence, and individuals in classes with lower adherence had greater baseline levels of depression, substance use concerns, and sexual risk. Differences in study satisfaction were also associated with adherence.

***Conclusions.*** This study supports the use of text-reported PrEP adherence. Identifying factors associated with less-than-optimal adherence may aid clinicians in anticipating at-risk patients requiring augmented intervention.

***Clinical trials registration.*** NCT01761643.

**Keywords.** PrEP; adherence; HIV; MSM; growth mixture modeling; text messaging.

Several randomized trials have examined oral tenofovir disoproxil fumarate (TDF), singly and in combination with emtricitabine (FTC), for human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP) among populations at elevated risk for HIV acquisition. Landmark studies such as iPrEx (Preexposure Prophylaxis Initiative) demonstrated significant reductions in HIV infection, and modeling studies suggest that consistent daily dosing with PrEP can result in near-absolute protection from HIV [1, 2]. Given convincing evidence of efficacy, PrEP use by HIV-uninfected individuals during periods of heightened risk promises to be an effective prevention tool in managing the HIV pandemic.

Underpinning PrEP usefulness is adherence. Post-hoc analyses have shown that high rates of protection in men who have sex with men (MSM) are most evident among those with drug concentrations corresponding to >4 doses per week [1, 2]. In contrast, in studies with overall low detectability, such as the PrEP Trial for HIV Prevention Among African Women (FEM-PrEP) and Vaginal and Oral Interventions to Control the Epidemic (VOICE) studies, poor adherence led to lack of efficacy [3, 4]. These null findings demonstrate the importance of adherence to PrEP and underscore the need to support adherence.

Although research on PrEP adherence interventions is nascent, some interventional approaches are promising. One low-cost and scalable intervention is short message service (SMS) technology—more widely known as "text-messaging" or "texting." Preliminary evidence suggests that text-messaging is efficacious in supporting PrEP adherence, and reviews have shown texting to improve adherence to antiretroviral therapy (ART) [5–8]. In addition to serving as an adherence intervention, 2-way text-messaging (ie, where participants are asked to reply to messages) doubles as an ecological momentary assessment (EMA) tool, permitting the collection of repeated observations at times closer to their real-time occurrence and in naturalistic settings [9]. Thus, 2-way texting has the ability to collect data integral to understanding variability in PrEP adherence in the context of everyday life.

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Although it is recognized that adherence may be heterogeneous, both across individuals at a given time and within individuals over time, little research has examined longitudinal patterns of variability in adherence and associated individual/contextual factors. Elucidating patterns of adherence over time may improve the ability to identify those at high risk for nonadherence, because of either static factors (eg, demographic characteristics) or modifiable psychosocial factors (eg, depression), who may benefit from interventional support. Consequently, this study aimed to examine the longitudinal PrEP adherence of individuals receiving daily text messages.

This study's goals were to (1) identify trajectories of PrEP adherence among individuals receiving adherence texts, (2) explore factors associated with patterns of adherence, and (3) examine study-end attitudes toward PrEP and the text-messaging intervention. A supplementary aim was to examine the utility of measuring PrEP adherence by using text-messaging as an EMA approach. It was hypothesized that, above and beyond demographic variables, psychosocial variables (ie, poorer social support, substance use, and depression) would be associated with classification in subgroups characterized by lower adherence. Additionally, it was hypothesized that subgroups with poorer text-reported adherence would have lower concentrations of the intracellular anabolites of PrEP and more-negative end-of-study attitudes (ie, beliefs of PrEP efficacy and satisfaction with study participation).

## METHODS

### Participants and Procedure

Participants were 181 MSM aged ≥18 years recruited from 4 southern California medical centers between February 2013 and February 2016 who were randomly assigned to the text-messaging arm of an open-label, randomized (1:1) clinical demonstration project for PrEP (California Collaborative Treatment Group 595—TAPIR study NCT01761643) [5]. Eligible participants reported substantial ongoing risk of HIV acquisition (ie, having at least 1 HIV-infected male sex partner for ≥4 weeks, no condom use during anal intercourse with ≥3 male partners who were HIV-positive/of unknown HIV status over the last 3 months, or no condom use during anal sex with ≥1 male partner and a sexually transmitted infection diagnosis in the last 3 months). The parent study aimed to determine the efficacy of a text-messaging intervention (Individualized Texting for Adherence Building [iTAB]), compared with standard of care.

Over a 48-week study period, all participants received once-daily TDF/FTC, risk reduction and adherence counseling, and safety monitoring. Participants in the iTAB arm also received daily text messages, coinciding with their intended dosing times, as supports for adherence. Message content varied and participants had choice in the types of messages they received, preselecting from a mix of health promotion and trivia domains. Each text message received was appended, "A) Took, D) Didn't, G) Snooze," and participants provided the appropriate adherence response; if participants responded "G," they were reminded by a text message sent an hour later. In the main study, iTAB participants were significantly more likely to have drug concentrations in dried blood spots (DBS) corresponding to a very high level of adherence [5]. Development of iTAB and its use among other populations has been described elsewhere [10].

The study protocol was approved by the relevant institutional review boards, and all participants provided informed consent after the nature of the study and possible consequences of participation were explained.

### Measures

#### *Baseline Predictor Variables*

***Substance use.*** Polysubstance use over the last month was assessed via computer-assisted self-interview, using a checklist; participants reported whether or not they used any of 11 substances (eg, cocaine, methamphetamine, and hallucinogens), and the number of substances used was totaled. Severity of problems resulting from substance use was assessed using the dichotomously scored Drug Abuse Screening Test–10 [11]. Reliability for the Drug Abuse Screening Test–10 was measured as an α value of 0.749.

***Poor social support.*** Poor social support was also measured via computer-assisted self-interview, using the 5-item modified Medical Outcomes Survey–Social Support Survey [12, 13]. Participants responded on a 4-point Likert scale ranging from "Strongly Disagree" (scored as 0) to "Strongly Agree" (scored as 3). Scores were averaged, and reliability was measured as an α value of 0.867.

***Depressive symptoms.*** Frequency of depressive symptoms over the past 2 weeks was assessed using the Patient Health Questionnaire [14]. Participants self-reported depressive symptoms on a 4-point scale ranging from "Not at All" (scored as 0) to "Nearly Every Day" (scored as 3), and scores were summed. Reliability was measured as an α value of 0.844.

***Condomless sex.*** Participants self-reported the number of instances of condomless receptive and insertive anal intercourse over the past 30 days.

#### *Adherence Outcomes*

***Self-reported PrEP adherence.*** Participants responded to daily text messages about PrEP adherence that were delivered via the iTAB messaging system. Each participant's daily responses of positive adherence were averaged across 4-week periods (ie, the numbers of "A" responses were summed across 4-week periods and divided by 28, with nonresponses scored as a "D"), yielding up to 12 measurements of monthly adherence. Missing data due to participant attrition were modeled under standard assumptions about missing data [15].

***Pharmacologic measures of adherence.*** Following established procedures, 25-μL aliquots of whole-blood samples collected at the end of the study (ie, during week 48 or, for participants lost to attrition, during the last visit while receiving treatment) were spotted onto filter paper to create DBS and were analyzed using liquid chromatography/tandem mass spectrometry [5, 16]. Adherence was estimated by measuring the concentration of tenofovir diphosphate (TFV-DP), an indicator of longer-term adherence (owing to its approximate half-life of 17 days), and the presence of emtricitabine triphosphate (FTC-TP), an indicator of shorter-term adherence (owing to its half-life of about 1.5 days), in intracellular peripheral blood mononuclear cell (PBMCs) [17]. Because of these differences in half-lives, the TFV-DP concentration was modeled continuously and FTC-TP detection was modeled dichotomously (ie, as undetectable vs detectable).

#### *End-of-Study Attitudes*

***PrEP efficacy.*** Participant beliefs about the efficacy of PrEP for HIV prevention were assessed using a single item and was scored on a scale from 0% to 100%.

***Study satisfaction.*** Satisfaction with text messages was measured using the mean score from 2 questions, with responses ranging from "Very Unsatisfied" (scored as 0) to "Very Satisfied" (scored as 10). Willingness to receive future messages was assessed using the mean score from 3 items, with responses ranging from "Not at All" (scored as 0) to "Very Much" (scored as 10). Items assessing satisfaction were highly correlated ($r = 0.716$), and the reliability of items assessing willingness was measured as an α level of 0.902.

#### Data Analytic Strategy

Growth mixture modeling (GMM), a technique of exploring heterogeneity and underlying (latent) classes, was used to examine patterns of self-reported adherence. Analyses followed stages of model specification, estimation, selection, and interpretation [18, 19]. First, a series of single-group models (intercept, linear slope, quadratic slope, and cubic slope models) were estimated to identify the overall longitudinal shape of adherence; goodness of fit was compared across nested models, using Satorra-Bentler $\chi^2$ difference tests [18–20]. Subsequently, models with increasing numbers of latent classes were specified, and comparisons of relative fit indices (Bayesian information criteria, entropy, and bootstrapped likelihood ratio test) were made to select for the best-fitting model.

Once the number of latent classes was determined, the influence of demographic characteristics on latent classification was examined. Between-class differences in pharmacologic measures of adherence (TFV-DP and FTC-TP) and end-of-study attitudes (PrEP efficacy and study satisfaction) were assessed using Wald $\chi^2$ tests; adjustments for multiple comparisons were made using the Benjamini-Hochberg procedure [21]. Additionally, multinomial regression was used to probe for psychosocial characteristics (ie, depressive symptoms, social support, and substance use) predicting group membership.

All models were estimated in Mplus 7.4, using robust maximum likelihood estimation. As the distribution of monthly adherence was negatively skewed with strong ceiling effects, adherence was modeled within GMMs, using Tobit modeling [15, 22, 23]. In Wald tests and multinomial regressions, a 3-step approach was used for acceptable estimation of standard errors and resistance against class shifts in the presence of covariates [24, 25].

## RESULTS

Over 57 795 participant-days, participants reported adherence on 85.10% of days, reported nonadherence on 0.08%, and did not respond on 14.10%. Correlations between types of adherence responses ("A," "D," and nonresponse) with TFV-DP and FTC-TP suggested that a greater number of "A" responses was associated with a higher TFV-DP concentration ($\rho = 0.356$; $P < .001$) and detectable FTC-TP ($\rho = 0.429$; $P < .001$). Conversely, more nonresponses were associated with a lower TFV-DP concentration ($\rho = -0.386$; $P < .001$) and undetectable FTC-TP ($\rho = -0.379$; $P < .001$), suggesting that nonresponse was associated with PrEP nonadherence. No significant associations between "D" responses and TFV-DP concentration or FTC-TP detection were observed, potentially owing to the low frequencies of "D" responses across the sample. Further descriptive statistics are provided in Tables 1 and 2.

#### Shape of Adherence Over Time

A number of single-group models were estimated to examine the shape of adherence over time, and log-likelihood difference tests indicated improved fit with increasing model complexity. As there was no significant difference in fit between a model with a cubic slope and one with a quadratic slope ($\chi^2_{(1)} = 0.159$; $P = .699$), the more parsimonious quadratic slope was chosen as the base model for subsequent analyses [19].

#### Estimating the Number of Classes

Through comparisons of fit indices of GMMs with 1–4 classes (Supplementary Table 1), a 4-class model was found to best fit the observed adherence responses (entropy, 0.901; bootstrapped likelihood ratio test statistic, 132.247; $P < .001$). Attempts to estimate a 5-class model were made; however, such a model did not converge on a proper solution and resulted in the formation of a class with a small sample size. Based on the pattern of adherence responses over time, the following 4 classes of adherence responses were established: class 1, denoting the highest adherence response frequency (ie, having consistent and near-perfect frequency); class 2, denoting the second highest frequency (ie, having consistent but less than perfect frequency); class 3, denoting a recovering frequency (ie, having an intermediate

**Table 1. Demographic Characteristics of 181 Participating Men Who Have Sex With Men**

| Characteristic | Value |
|---|---|
| Age, y, mean ± SD | 34.98 ± 10.05 |
| Education level | |
| High school or less | 16 (8.80) |
| Some college | 69 (38.10) |
| Bachelor's degree | 62 (34.30) |
| Some postgraduate | 5 (2.80) |
| Advanced degree | 29 (16.00) |
| Race | |
| White | 146 (80.66) |
| Black | 27 (14.92) |
| Other | 8 (4.42) |
| Hispanic ethnicity | 52 (28.73) |
| Monthly income, $ | |
| <2000 | 38 (21.00) |
| ≥2000 | 105 (58.00) |
| Decline to state/missing | 38 (21.00) |
| Recruitment site | |
| University of California–San Diego | 81 (44.80) |
| Harbor-UCLA | 22 (12.20) |
| Long Beach | 17 (9.40) |
| University of Southern California | 61 (33.70) |

Data are no. (%) of subjects, unless otherwise indicated.

frequency that declined and then recovered toward the end of the study); and class 4, denoting the lowest frequency (ie, having the lowest and declining adherence frequency). Figure 1 depicts these adherence classes.

The influences of demographic variables (ie, age, location, income, race, and education level) were examined, and age and race were found to be significantly associated with class. In particular, relative to individuals in class 1, those in class 2 (OR, 0.951; $P = .040$) and class 3 (OR, 0.942; $P = .020$) were less likely to be older, while those in class 4 (OR, 3.842; $P = .032$) were more likely to be nonwhite. As such, age and race were included as covariates affecting class. The overall pattern of adherence and interpretation of the 4 classes remained similar, with 66 individuals (36%) in class 1, 47 (26%) in class 2, 38 (21%) in class 3, and 30 (17%) in class 4. Supplementary Table 1 also details this covariate-adjusted model.

#### Class Differences in PrEP DBS Levels

Class-specific differences in mean DBS levels were examined (Table 3). Omnibus $\chi^2$ tests indicated significant differences in TFV-DP and FTC-TP ($P$s < .001). With regard to TFV-DP concentration, significant differences were observed between class 1 and class 4 and class 1 and class 3 (class 1 > class 4 and class 1 > class 3; adjusted $P$s < .05), such that classes with higher iTAB-reported adherence had significantly higher TFV-DP concentrations. At the end of the study, the proportions of individuals per class with TFV-DP concentrations ≥774 fmol (indicating receipt of approximately 4 doses of PrEP in the last week) and 1389 fmol (indicating receipt of approximately 7 doses of PrEP in the last week) were 86% and 53%, respectively, in class 1; 83% and 40%, respectively, in class 2; 76% and 16%, respectively, in class 3; and 47% and 20%, respectively, in class 4 [26]. Regarding FTC-TP detection, the omnibus $\chi^2$ test yielded a $P$ value of <.001, indicating statistically significant differences in the frequencies of detectability across classes. These differences were between class 1 and class 4, class 2 and class 4, and class 3 and class 4 (class 1 > class 4, class 2 > class 4, and class 3 > class 4; adjusted $P$s < .001). Thus, undetectable FTC-TP was more frequent among individuals in class 4.

#### Class Differences in End-of-Study Attitudes

Differences in attitudes related to PrEP efficacy and study satisfaction with were also examined (Table 3). The result of an omnibus $\chi^2$ test of beliefs about PrEP efficacy was statistically significant ($P < .05$), and individuals in classes with the highest adherence generally reported holding greater beliefs about PrEP efficacy; however, differences were marginally significant after controlling for multiple comparisons. Regarding satisfaction with text messages received, the omnibus $\chi^2$ test yielded a statistically significant result ($P < .05$), and significant differences were found between class 2 and class 3 and between class 2 and class 4 (class 2 > class 3 and class 2 > class 4; adjusted $P$s < .05). Regarding willingness to use the text-messaging reminder system in the future, the result of the omnibus $\chi^2$ test was statistically significant ($P < .05$), and individuals in class 2 tended to have greater willingness to receive future messages; however, differences were marginally significant after adjustment for multiple comparisons.

#### Predictors of Adherence Classes

Table 4 reports results of multinomial regressions of latent classes on psychosocial risk factors. Relative to individuals in class 1, individuals in class 2 were more likely to report condomless sex (OR, 1.073; $P = .029$). Compared with individuals in class 1, individuals in class 4 were more likely to have depressive symptoms (OR, 1.111; $P = .039$), to have severe substance use problems (OR, 1.373; $P = .005$), and to use more substances (OR, 1.332; $P = .049$). Additionally, compared with individuals in class 1, individuals in class 3 were more likely to have severe substance use problems (OR, 1.305; $P = .007$), to use more substances (OR, 1.536; $P = .001$), and to have condomless sex (OR, 1.073; $P = .032$). Marginal effects were found for social support, such that individuals in lower adherence classes tended to have poorer social support.

## DISCUSSION

Despite heterogeneity in PrEP adherence, little research has examined patterns of variability and factors associated with longitudinal use. In a 48-week text-messaging–based study of PrEP adherence, GMM was used to identify subgroups with differing

**Table 2. Descriptive Statistics of Study Variables**

| Variable | Subjects, No. | Value[a] | Range |
|---|---|---|---|
| iTAB-measured adherence, subjects, % | | | |
| Overall | 181 | 84.53 ± 14.04 | 30.00–99.00 |
| Month 1 | 181 | 96.43 (85.71–100.00) | 0.00–100.00 |
| Month 2 | 181 | 92.86 (82.14–96.43) | 10.71–100.00 |
| Month 3 | 181 | 92.86 (78.57–100.00) | 21.43–100.00 |
| Month 4 | 172 | 92.86 (78.57–100.00) | 17.86–100.00 |
| Month 5 | 172 | 91.07 (78.57–96.43) | 3.57–100.00 |
| Month 6 | 172 | 89.29 (75.00–96.43) | 0.00–100.00 |
| Month 7 | 167 | 89.29 (71.43–96.43) | 25.00–100.00 |
| Month 8 | 167 | 89.29 (71.43–96.43) | 7.14–100.00 |
| Month 9 | 166 | 89.29 (74.11–96.43) | 0.00–100.00 |
| Month 10 | 153 | 89.29 (78.57–96.43) | 0.00–100.00 |
| Month 11 | 151 | 89.29 (78.57–96.43) | 14.29–100.00 |
| Month 12 | 150 | 89.29 (75.00–96.43) | 14.29–100.00 |
| Pharmacologically measured adherence | | | |
| TFV-DP level, fmol | 178 | 1224.50 (832.00–1526.50) | 90–2968 |
| Undetectable FTC-TP, subjects, no. (%) | 181 | 25 (13.80) | … |
| Psychosocial factors | | | |
| Depressive symptom severity (summed score), subjects, no. (%) | | 5.19 (4.93) | 0–26 |
| None (0–4) | 179 | 92 (51.40) | … |
| Mild (5–9) | 179 | 57 (31.80) | … |
| Moderate (10–14) | 179 | 22 (12.30) | … |
| Moderately severe—severe (≥15) | 179 | 8 (4.50) | … |
| Illicit substances used, no. | 179 | 1.94 ± 1.93 | 0–7 |
| Problems with substances, score | 179 | 1.71 ± 1.90 | 0–10 |
| Poor social support, score | 179 | 0.72 ± 0.68 | 0–3 |
| Condomless sex, instances, no. | 147 | 5.32 ± 10.75 | 1–102 |
| End-of-study attitudes, score | | | |
| PrEP efficacy | 144 | 93.74 ± 10.21 | 83.20–100.00 |
| Satisfaction with text messages | 143 | 8.75 ± 2.02 | 1.00–10.00 |
| Willingness to receive future messages | 143 | 8.58 ± 2.25 | 1.00–10.00 |

Abbreviations: FTC-TP, emtricitabine triphosphate; iTAB, Individualized Texting for Adherence Building; PrEP, preexposure prophylaxis; TFV-DP, tenofovir diphosphate.

[a]Data are mean ± SD or median (interquartile range), unless otherwise indicated.

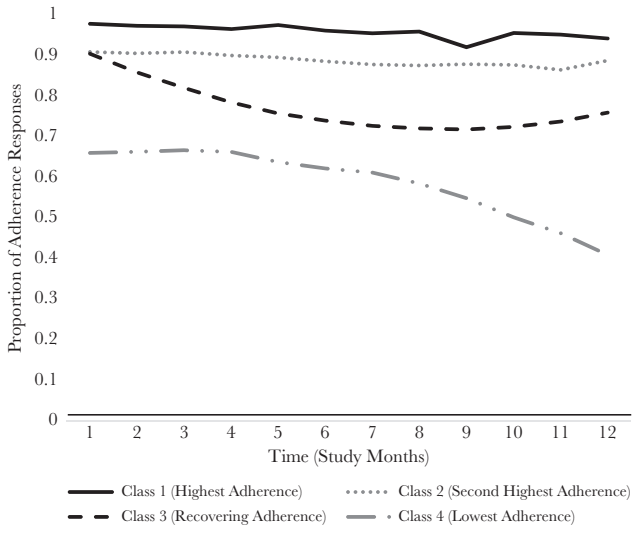


**Figure 1.** Adherence response proportions determined by the Individualized Texting for Adherence Building (iTAB) intervention across the 4 latent classes over time.

adherence profiles, baseline predictors of adherence, and related end-of-study attitudes. GMM identified 4 subgroups with distinct patterns of adherence over time: 2 classes with consistently high adherence, 1 class with intermediate levels of adherence that decreased and recovered slightly, and 1 class with relatively low initial levels of adherence that declined over time.

Text-reported adherence correlated with TFV-DP concentration and FTC-TP detection. Regarding TFV-DP, individuals in class 1 had mean concentrations consistent with near-perfect adherence (approximately 6–7 doses per week), while those in class 2 had concentrations consistent with good adherence (approximately 5–6 doses per week); individuals in class 3 and class 4 had mean concentrations consistent with adequate but less-than-optimal adherence (approximately 4–5 doses per week) [26]. Generally, classes with the highest text-reported adherence had a greater frequency of FTC-TP detection and a lower frequency of FTC-TP nondetection. As has been observed in other studies, TFV-DP may be preferable to FTC-TP for assessing longer-term adherence, owing to its lengthier half-life

**Table 3. Between-Class Differences in End-of-Study Variables**

| Variable | Class 1 | Class 2 | Class 3 | Class 4 | Omnibus Test Result | |
|---|---|---|---|---|---|---|
| | | | | | $\chi^2$ | *P* |
| Pharmacologically measured adherence | | | | | | |
| TFV-DP level, fmol | 1424.175 ± 60.430 | 1232.648 ± 103.542 | 1039.334 ± 112.436 | 993.709 ± 55.491 | 17.539[a] | < .001 |
| Undetectable FTC-TP, subjects, no. | 1 | 3 | 4 | 17 | 58.667[b] | < .001 |
| Belief about PrEP | | | | | | |
| PrEP efficacy, score | 95.529 ± 0.657 | 96.665 ± 0.757 | 93.035 ± 1.635 | 82.266 ± 5.871 | 9.738[c] | .021 |
| iTAB feedback | | | | | | |
| Satisfaction with intervention, score | 8.697 ± 0.307 | 9.444 ± 0.203 | 8.178 ± 0.422 | 8.282 ± 0.434 | 12.683[d] | .005 |
| Willingness to use again, score | 8.374 ± 0.344 | 9.315 ± 0.226 | 8.303 ± 0.412 | 7.839 ± 0.671 | 10.547[e] | .014 |

Data are mean ± standard error, unless otherwise indicated.

Abbreviations: FTC-TP, emtricitabine triphosphate; iTAB, Individualized Texting for Adherence Building; PrEP, preexposure prophylaxis; TFV-DP, tenofovir diphosphate.

[a]Significant differences were observed between classes 1 and 3 ($\chi^2_{(1)}$ = 9.963; adjusted *P* = .012) and classes 1 and 4 ($\chi^2_{(1)}$ = 6.577; adjusted *P* = .030).

[b]Significant differences were observed between classes 1 and 4 ($\chi^2_{(1)}$ = 41.626; adjusted *P* < .001), classes 2 and 4 ($\chi^2_{(1)}$ = 25.238; adjusted *P* < .001), and classes 3 and 4 ($\chi^2_{(1)}$ = 17.697; adjusted *P* < .001).

[c]Marginally significant differences were observed between classes 1 and 4 ($\chi^2_{(1)}$ = 5.042; adjusted *P* = .075) and classes 2 and 4 ($\chi^2_{(1)}$ = 5.913; adjusted *P* = .075).

[d]Significant differences were observed between classes 2 and 3 ($\chi^2_{(1)}$ = 6.881; adjusted *P* = .045) and classes 2 and 4 ($\chi^2_{(1)}$ = 5.930; adjusted *P* = .045); marginal differences were observed between classes 1 and 2 ($\chi^2_{(1)}$ = 4.534; adjusted *P* = .066).

[e]Marginally significant differences were observed between classes 1 and 2 ($\chi^2_{(1)}$ = 5.287; adjusted *P* = .074), classes 2 and 4 ($\chi^2_{(1)}$ = 4.368; adjusted *P* = .074), and classes 2 and 3 ($\chi^2_{(1)}$ = 4.589; adjusted *P* = .074).

and robustness against recent dosing in anticipation of a medical visit (ie, "white coat adherence") [27]. However, FTC-TP can also be a useful indicator of recent nonadherence, as detectable/undetectable FTC-TP can provide information about whether dosing occurred within the last 48 hours [17]. Thus, TFV-DP and FTC-TP may provide complementary data about adherence behaviors.

In line with other PrEP studies, younger age was related to poorer text-reported adherence. Additionally, being a racial minority (predominantly African American, in our sample) was associated with poorer self-report of adherence [28–30]. Multiple studies have drawn links between sociostructural barriers, including medical mistrust, stigma, and low health literacy, and poorer adherence to HIV medications among African Americans [31–33]. Given elevated contextual vulnerability to HIV infection, lower rates of PrEP adherence among African Americans in adherence studies highlight the need to adapt interventions to address some of the unique barriers faced by African Americans.

**Table 4. Regression Estimates Obtained from Multinomial Models Examining Predictors of Classification**

| Characteristic | Odds Ratio (95% Confidence Interval) | | |
|---|---|---|---|
| | Class 2 | Class 3 | Class 4 |
| Depressive symptoms | 1.030 (.929–1.143) | 1.049 (.957–1.150) | 1.111[b] (1.005–1.227) |
| Age | 0.951[b] (.906–.999) | 0.942[b] (.895–.991) | 0.969 (.914–1.028) |
| Race | 3.093[a] (.868–11.013) | 1.895 (.517–6.948) | 3.842[b] (1.118–13.208) |
| Poor social support | 0.769 (.369–1.600) | 1.726[a] (.929–3.207) | 1.737[a] (.980–3.078) |
| Age | 0.951[b] (.906–.999) | 0.942[b] (.895–.991) | 0.969 (.914–1.028) |
| Race | 3.093[a] (.868–11.013) | 1.895 (.517–6.948) | 3.842[b] (1.118–13.208) |
| Severity of substance use | 1.054 (.845–1.316) | 1.305[c] (1.077–1.581) | 1.373[c] (1.102–1.710) |
| Age | 0.951[b] (.906–.999) | 0.942[b] (.895–.991) | 0.969 (.914–1.028) |
| Race | 3.093 (.868–11.013) | 1.895 (.517–6.948) | 3.842[b] (1.118–13.208) |
| No. of substances used | 1.276[a] (.971–1.676) | 1.536[c] (1.193–1.978) | 1.332[b] (1.001–1.774) |
| Age | 0.951[b] (.906–.999) | 0.942[b] (.895–.991) | 0.969 (.914–1.028) |
| Race | 3.093[a] (.868–11.013) | 1.895 (.517–6.948) | 3.842[b] (1.118–13.208) |
| Condomless sex | 1.073[b] (1.007–1.142) | 1.073[b] (1.005–1.144) | 1.066[a] (1.001–1.135) |
| Age | 0.951[b] (.906–.999) | 0.942[b] (.895–.991) | 0.969 (.914–1.028) |
| Race | 3.093[a] (.868–11.013) | 1.895 (.517–6.948) | 3.842[b] (1.118–13.208) |

Estimates are relative to class 1.

[a].05 < *P* < .10.

[b].01 < *P* < .05.

[c].001 < *P* < .01.

Additionally, individuals in classes with lower adherence were more likely to have greater levels of depression and substance use concerns. These results are consistent with other findings of negative effects of psychosocial risk factors on adherence [34]. Of note, individuals in class 2 were most likely to approve of the text-messaging intervention and also had a multiple risk factors (ie, sexual risk, depression, younger age, substance use). The greater acceptability of the intervention among this at-risk group, concomitant with their sustained levels of adherence, suggests that text-messaging supports adherence among individuals at higher risk of HIV exposure.

Importantly, this study expands the literature on PrEP adherence by examining adherence trajectories and predictors of variability, using methods consistent with person-centered models of change. Identifying discrete subpopulations of individuals following similar adherence courses and predictors of classification may aid in identifying those at risk for nonadherence who may require increased interventional support. Although all participants examined in this study received text messages to support their adherence, findings of adverse effects from modifiable factors, such as substance use and depressive symptoms, suggest the need to bolster adherence interventions with supportive psychosocial components. Among the limited enhanced PrEP studies, counseling has been shown to support adherence [35, 36]. Future text-messaging interventions should take advantage of their ability to simultaneously monitor adherence and factors relevant to adherence in an ongoing fashion and, potentially, intervene if the risk for nonadherence develops. Indeed, ongoing assessment has been successfully used to identify when the intensity of interventions should be idiographically scaled up or down, both in supportive interventions for ART adherence, as well as in just-in-time adaptive interventions for other health behavior change [37, 38]. In addition to potentially decreasing new HIV infections among those who are inadequately adherent to PrEP, identifying those at risk for poor adherence and providing timely intervention may also increase the cost-effectiveness of PrEP implementation [39, 40].

Previous work has compared retrospective self-report to pharmacologically measured adherence and found evidence of over-estimation of adherence via retrospective self-report [4]. This study, however, provides some support for self-report via text-messaging, given the concordance of daily text message summaries and TFV-DP concentration. A strength of text-messaging as an EMA approach over global retrospective recall is that it provides means of obtaining more-accurate assessments of daily behavior by limiting the effect of various recall biases [9, 41]. Although daily self-report may also be impacted by social desirability or other demand characteristics, the correspondence of measures suggests that, when individuals respond to daily text messages, they are able to relatively accurately report on their adherence behaviors. Furthermore, this study suggests that sustained nonresponse (in addition to continued responses of nonadherence) may signal adherence concerns. Future studies should consider nonresponse as valuable to assessing the risk for nonadherence.

This study has several limitations. First, as participants were enrolled in an interventional study, their longitudinal adherence may not generalize to real-world settings where adherence support is less structured. Second, the relatively high adherence rates may also reflect participants' eagerness to receive PrEP at a time when availability and coverage by insurance was limited. Furthermore, we considered nonresponse to text messages as nonadherence to PrEP, potentially overestimating true PrEP nonadherence. For instance, a discrepancy between pharmacologically measured PrEP adherence and the number of responses by text was most evident for individuals in the class with the lowest frequency of text-reported adherence (class 4), whose model-estimated adherence in the last month of the study was approximately 41% and below what would be anticipated from the class-specific average TFV-DP concentration, which indicated adherence between 57% and 71% [26]. However, as there was an inverse relationship between the number of nonresponses and pharmacologically measured adherence, nonresponse and nonadherence are likely highly related. Future studies should incorporate measures to parse these two adherence behaviors (ie, adherence to PrEP and adherence to the study protocol).

In summary, this study contributes to the expanding literature on PrEP adherence and demonstrates text-messaging as a useful approach for capturing longitudinal adherence among HIV-uninfected MSM. Future research should investigate the association of adherence trajectories with dynamic and more-frequently assessed correlates to better understand PrEP adherence in the context of high-risk sexual behavior.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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