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AIDS and Behavior (2025) 29:2483–2494
https://doi.org/10.1007/s10461-025-04709-8

ORIGINAL PAPER

The Association Between Use of Adherence Support Interventions and Adherence to HIV Preexposure Prophylaxis Among Young South African and Zimbabwean Women in HPTN 082

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Accepted: 27 March 2025 / Published online: 10 April 2025
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Abstract

We assessed the association between PrEP adherence support interventions and intracellular tenofovir-diphosphate (TFV-DP) levels, a biomarker for PrEP adherence, using data from 368 South African and Zimbabwean adolescent girls and young women enrolled in the HIV Prevention Trials Network 082 trial from 2016 to 2018. Group-based trajectory modeling identified trajectories of TFV-DP levels and adherence support interventions, including weekly two-way SMS and optional monthly adherence clubs. Two trajectories of TFV-DP levels were identified: a consistently low trajectory (N = 248, 67.4%, with consistent TFV-DP levels of 100 fmol/punch) and a high-decreasing trajectory (N = 120, 32.6%, with TFV-DP levels decreasing from approximately 900 to 500 fmol/punch). Two trajectories were also observed for adherence club attendance: consistently moderate (N = 249, 67.7%, attended approximately two out of three clubs in a three-month period) and low-increasing (N = 119, 32.3%). Similarly, SMS response patterns included a consistently high engagement group (N = 222, 66.1%), who responded to approximately 90% of messages, and a consistently low engagement group (N = 114, 33.9%). Women with consistently high SMS responses had higher odds of being in the high-decreasing TFV-DP levels trajectory group (Adjusted Odds Ratio [AOR]: 6.6; 95% CI 2.8–15.5; $p < 0.001$), while those with a consistently moderate adherence club attendance trajectory had an AOR of 1.3 (95% CI 0.5–3.3, $p = 0.620$) for being in the same group. Use of PrEP was aligned with the higher response trajectories of SMS responses but not with attendance to adherence support clubs.

Keywords HIV · Pre-exposure prophylaxis · Adherence support clubs · Two-way SMS · Sub-Saharan Africa · Adolescent girls and young women

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Introduction

Adolescent girls and young women (AGYW) aged 15–24 remain at a disproportionately high risk of acquiring HIV in Sub-Saharan Africa (SSA), where they accounted for more than 77% of young people aged 15–24 newly diagnosed with HIV in 2022 [1]. Oral pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir (FTC/TDF) is highly effective in men and women when taken as prescribed, and it could significantly reduce HIV acquisition among African AGYW [2].

One of the biggest challenges with oral PrEP is maintaining sufficient adherence to daily pill-taking, especially among younger populations. Several factors contribute to poor PrEP adherence among African AGYW, including lack of social support, stigma related to sexual activity and

antiretroviral medications, depression, gender-based violence, and concerns about medication safety [3–6]. Adherence to PrEP is likely a dynamic process, influenced by changes in risk behaviors, perceived HIV risk, motivation, and the ability to take pills consistently. Multi-level adherence support interventions may enhance the effectiveness of PrEP among AGYW [7].

Two-way SMS is an interactive communication method between clients and healthcare providers that can enhance support, boost motivation, and improve medication adherence [8]. In the context of PrEP, it enables real-time communication, allowing healthcare providers to address women's concerns about medication use and potential side effects, which may improve adherence [9]. Adherence clubs represent another promising strategy by offering a supportive environment where participants can better understand medication use, navigate family and partner relationship challenges, and overcome stigma-related barriers to HIV prevention. Through peer support and normalization of PrEP use, these clubs help individuals remain engaged in care [10, 11].

An early PrEP demonstration study, HPTN 082, assessed weekly 2-way SMS, brief counseling, and optional peer-led PrEP adherence clubs as standard of care adherence support interventions in comparison to the impact of TFV-DP levels in DBS feedback counseling among AGYW in addition to standard adherence support [12]. The trial found no significant difference in PrEP adherence between participants who received drug-level feedback and those who did not. However, gaps remain in understanding whether PrEP adherence was associated with the dose or extent of participation in other standard adherence support interventions.

Group-based trajectory modeling (GBTM) is a novel methodological approach used to analyze the trajectories of an outcome of interest over time [13]. Rather than classifying individuals simply as adherent or non-adherent, GBTM identifies subgroups of individuals who follow distinct adherence patterns. This method has been increasingly applied across various disease states, often identifying four to six distinct adherence trajectories [14]. In the context of PrEP, characterizing TFV-DP levels trajectories may help identify predictors of adherence patterns, allowing for tailored interventions that are more scalable and targeted toward individuals at risk of poor adherence [15].

GBTM could provide informative data by identifying trajectories of PrEP adherence support interventions use and whether exposure to these interventions was associated with PrEP drug levels. Specifically, we hypothesized that GBTM analysis would identify distinct latent trajectories of TFV-DP levels and adherence support interventions in the HPTN 082 study and that these trajectories would be associated with engagement in adherence support interventions, including peer-led adherence clubs and weekly two-way SMS.

Methods

Study Design

We conducted a retrospective analysis of data from the HPTN 082 trial, an open-label study evaluating oral PrEP uptake and adherence support interventions. The trial was conducted at three sites in Sub-Saharan Africa—Johannesburg and Cape Town, South Africa, and Harare, Zimbabwe—from October 2016 to October 2018.

Study Participants

Eligible participants were AGYW who were literate, assigned female at birth, aged 16–25 years, HIV-negative, and sexually active (defined as vaginal or anal intercourse in the month prior to screening). Participants were also required to have a VOICE risk score > 5 [16], express interest in taking PrEP, and have access to a mobile phone capable of receiving SMS. Additional eligibility criteria included being hepatitis B seronegative (and willing to receive vaccination if not immune), having normal renal function (creatinine clearance > 60 ml/min), and not being pregnant.

Procedures

At enrollment, participants who accepted PrEP were provided with daily oral PrEP and were randomized in a 1:1 ratio to receive either standard adherence support or enhanced adherence support, which included TFV-DP level feedback counseling in addition to the standard support [12].

Demographic data collected at enrollment included age and educational attainment. At baseline and follow-up visits, participants completed a computer-assisted self-interview questionnaire assessing sexual behavior (e.g., condom use, number of sexual partners), perceived risk of HIV and pregnancy over the next year, alcohol use [17], drug use, HIV- and PrEP-related stigma [18–20] (Supplemental Table 1), social support [21, 22] (Supplemental Table 2), intimate partner violence [23] (Supplemental Table 3), and depressive symptoms [24]. Participants were followed for 52 weeks, with visits at weeks 4, 8, 13, 26, 39, and 52. All participants received PrEP adherence counseling at each visit. Those in the intervention arm received additional adherence feedback counseling based on TFV-DP levels at weeks 8 and 13. A one-month supply of PrEP was dispensed at each of the first three monthly visits, and a three-month

supply was provided at subsequent quarterly visits (details described elsewhere) [12].

PrEP Adherence Support Interventions

All participants received automated weekly two-way SMS messages during the first 13 weeks of the study. These messages focused on participants' general well-being rather than PrEP adherence, to avoid inadvertent PrEP disclosure. Participants were also asked whether they wanted to speak with a staff member (e.g., about side effects). The message read: "Hey sister, are you OK? Type YES or NO," based on the WelTel model of SMS-based adherence support [25]. If no response was received, a reminder was sent the following day. Participants who either did not respond or responded "No" were contacted by phone so that staff could address any concerns. For this analysis, SMS engagement was defined as responding "Yes" or "No" to at least one message; non-engagement was defined as failing to respond to both the initial and follow-up message.

Participants were also offered the opportunity to join optional monthly adherence support clubs, facilitated by HPTN 082 participants at each study site. These peer-led clubs were designed to create a supportive space for participants to discuss PrEP use, adherence challenges, and relationship issues that could impact adherence. Participants were encouraged to help shape the activities of the adherence clubs, which were centered around PrEP use and aimed to foster interaction among participants and with study staff, thereby promoting social connection and support. Through these interactions, participants shared their experiences with PrEP, facilitating mutual learning. Trial staff supported the clubs by guiding discussions and addressing any clinical or technical questions related to PrEP. At each follow-up visit, participants self-reported how frequently they attended the peer-led adherence clubs.

In this analysis, we did not assess the effect of the drug level feedback strategy provided to participants in the enhanced adherence support arm at months 1 and 2, as no significant differences in TFV-DP levels were observed between the enhanced and standard support arms at months 3, 6, or 12.

Outcome Measurement

Intracellular TFV-DP levels were measured in DBS at the University of Cape Town, which validated the DBS testing in partnership with the University of Colorado Pharmacology laboratory, the developer of the TFV-DP in DBS assay [26]. The University of Colorado measured TFV-DP levels in DBS as an objective marker of adherence over the previous 6–8 weeks [26, 27]. Intracellular TFV-DP in red blood cells has a 17-day half-life and a 25-fold drug accumulation. TFV-DP levels were collected at weeks 13, 26, and 52.

Statistical Analysis

We included participants who had at least two TFV-DP level measurements during the 52-week follow-up period. To analyze adherence club attendance, we calculated a monthly attendance rate by dividing the number of reported club visits at each follow-up by the number of months since the previous visit.

Descriptive statistics were used to summarize categorical variables as counts and percentages, and continuous variables as medians with interquartile ranges (IQRs) within each TFV-DP levels trajectory group. The Chi-square test or Kruskal–Wallis test was used to compare baseline characteristics across TFV-DP levels trajectory groups, as appropriate. The Chi-square test was also used to determine associations between TFV-DP levels trajectories and trajectories of adherence support interventions (peer support clubs and SMS). A p-value < 0.05 was considered statistically significant.

Group-Based Trajectory Modeling

GBTM applies finite mixture models and maximum likelihood estimation to delineate latent groups of individuals who exhibit similar patterns of certain behavior over time, with intercepts and slopes determining the trajectory of each group. The intercept represents the baseline score, while the slope represents the rate of change of the trajectory across assessments. Trajectory shapes are described by a polynomial function (quadratic or cubic) of time [28]. We used GBTM to identify latent homogenous groups of attendance in peer support monthly adherence clubs (6 assessments on monthly attendance rate), intracellular TFV-DP levels (measured at weeks 13, 26, and 52), and SMS trajectories (assessed weekly for the first 13 weeks). Given the differing measurement schedules across outcomes, we modeled each variable separately using GBTM rather than applying group-based multi-trajectory modeling. This approach allowed for accurate modeling aligned with the unique timing of assessments for each outcome.

Adherence club attendance and TFV-DP levels were treated as continuous variables and modeled using censored normal finite mixture models. SMS engagement was treated as a categorical variable and modeled using a logit function. We sequentially fit various models to determine the optimal number of latent groups, considering constant, linear, quadratic, and cubic specifications and performing visual inspections of fit. Model selection was based on a combination of the following criteria: (1) Bayesian Information

Criterion (BIC), with lower values indicating better fit; (2) entropy, with mean posterior probabilities > 0.70 suggesting acceptable classification; (3) group sizes of at least 5% of the total sample; (4) narrow confidence intervals around estimated group membership probabilities; and (5) parsimony, favoring simpler models with fewer classes and parameter probabilities [29].

We assumed that the missingness was missing at random. Under this assumption, missingness is accommodated by GBTM by fitting the model using maximum likelihood estimation and, therefore, producing asymptotically unbiased parameter estimates. All statistical analyses were conducted using Stata software, version 17 (Stata Corp LLC, College Station, TX), and Stata Plugin was used to estimate GBTM parameters [30].

Logistic Regression Analysis

Logistic regressions were performed to assess unadjusted associations between covariates and the outcome. To balance variable retention with model parsimony, covariates with p-values ≤ 0.1 were selected for inclusion in the final multivariate model. A p value < 0.05 was considered statistically significant.

Ethics Review

The study received ethical approval from institutional review boards at each participating site. Written informed consent was obtained from all participants in either English or the participant's local language. For girls under 18 years of age, assent and parental or guardian consent were obtained when required by local regulations.

Results

Of the 427 participants who initiated PrEP in HPTN 082, 368 were included in this analysis. Among the excluded, 30 participants (7.0%) were lost to follow-up and 29 (6.7%) had fewer than two TFV-DP level measurements during follow-up. Nearly two-thirds of participants were over 20 years old, and 319 (86.6%) had completed secondary education. The majority (85.9%) reported having a primary sex partner in the past three months, and nearly half reported not using a condom during vaginal sex in the past month. Half of the participants perceived themselves to be at no risk of acquiring HIV in the next year, and nearly half also believed they were not at risk of becoming pregnant during the same period. The median VOICE risk score was 7 (interquartile range [IQR]: 6–8), and 189 participants (51.4%) reported symptoms of depression at baseline (Table 1).

Of the 368 participants included, 338 (91.8%) remained in the study through week 52. A total of 1,049 TFV-DP level measurements were collected: 355 (33.8%) at week 13, 356 (33.9%) at week 26, and 338 (32.2%) at week 52. TFV-DP levels above 700 fmol/punch were detected in 90 participants (25.3%) at week 13, declining to 75 (21.0%) at week 26 and 27 (8.0%) at week 52.

PrEP Adherence Trajectories

GBTM identified two latent TFV-DP levels trajectories. The first group (N = 248, 67.4%) followed a consistently low trajectory, with TFV-DP levels remaining around 100 fmol/punch. The second group (N = 120, 32.6%) showed a high-decreasing trajectory, starting at approximately 900 fmol/punch and declining to 500 fmol/punch over time (Fig. 1).

Women in the consistently low group were more likely to be younger, with a greater proportion under 20 years of age ($\chi^2 = 7.24$, p = 0.007). They also tended to perceive themselves as having no or low HIV risk. In contrast, women in the high-decreasing group were more likely to perceive a moderate or high chance of acquiring HIV ($\chi^2 = 10.80$, p = 0.01) (Table 1).

Trajectories of Adherence Support Interventions

Two adherence club attendance trajectories were identified. The first group (N = 249, 67.7%) had consistently moderate attendance, participating in approximately two out of every three monthly meetings. The second group (N = 119, 32.3%) followed a low-increasing attendance pattern (Fig. 2). For SMS responses, two trajectories were also identified. The first group (N = 222, 66.1%) had consistently high engagement, responding to approximately 90% of messages. The second group (N = 114, 33.9%) had consistently low engagement (Fig. 3).

Logistic Regression Analysis

Table 2 summarizes the predictors of membership in the high-decreasing TFV-DP levels trajectory group. In unadjusted models, higher adherence was associated with study site, age, educational attainment, and perceived HIV risk. Engagement in adherence support interventions, including SMS response and adherence club attendance, also showed associations and social support showed a modest association.

In the multivariable analysis, study site remained a strong predictor of adherence. Participants from Harare, Zimbabwe had significantly higher odds of adherence (Adjusted Odds Ratio [AOR]: 10.2; 95% CI 3.5–29.2; p < 0.001), as did those from Johannesburg, South Africa (AOR: 4.1; 95%

Table 1 Participant characteristics at baseline across TFV-DP levels in DBS trajectory groups

Background characteristics	Trajectory groups of TFV-DP levels in DBS			Test statistics Value	P value
	Consistently low (n=248)	High decreasing (n=120)	Total (n=368)		
Study site					
Cape Town, South Africa	102 (41.1)	28 (23.3)	130	$\chi^2=15.2051$	<0.001
Harare, Zimbabwe	67 (27.0)	54 (45.0)	121		
Johannesburg, South Africa	79 (31.9)	38 (31.7)	117		
Treatment arm					
Standard adherence	125 (50.4)	59 (49.2)	184	$\chi^2=0.0495$	0.824
Enhanced adherence	123 (49.6)	61 (50.8)	184		
Age groups					
<20 years	95 (38.3)	29 (24.2)	124	$\chi^2=7.2369$	0.007
>=20 years	153 (61.7)	91 (75.8)	244		
Education					
College or university	32 (12.9)	9 (7.5)	41	$\chi^2=8.6747$	0.013
Secondary school	214 (86.3)	105 (87.5)	319		
Primary school	2 (0.8)	6 (5.0)	8		
Primary sex partner in past 3 months (n=355)					
No	38 (16.1)	12 (10.1)	50	$\chi^2=2.3674$	0.124
Yes	198 (83.9)	107 (89.9)	305		
Perceived risk of getting HIV in the next year (n=344)					
No risk at all	129 (56.3)	44 (37.9)	173	$\chi^2=10.8010$	0.013
Small chance	65 (28.4)	48 (41.4)	113		
Moderate chance	15 (6.6)	12 (10.3)	27		
Great chance	20 (8.7)	12 (10.3)	32		
Condom use with vaginal sex, past month (n=272)					
No	95 (54.0)	59 (61.5)	154	$\chi^2=2.8162$	0.245
Part of the last time	7 (3.9)	6 (6.3)	13		
Yes	74 (42.1)	31 (32.2)	105		
Primary partner's HIV status (n=241)					
HIV negative	118 (78.7)	63 (69.2)	181	$\chi^2=2.9359$	0.230
HIV positive	2 (1.3)	1 (1.1)	3		
Don't know	30 (20.0)	27 (29.7)	57		
Primary sex partner had sex with anyone besides you in the past 3 months (n=302)					
No	39 (19.9)	21 (19.8)	60	$\chi^2=1.1668$	0.558
Yes	59 (30.1)	38 (35.9)	97		
Don't know	98 (50.0)	47 (44.3)	145		
Risk of pregnancy in the next year (n=344)					
Not at risk	101 (44.5)	60 (51.3)	161	$\chi^2=4.0765$	0.253
Small chance	78 (34.4)	38 (32.5)	116		
Moderate chance	28 (12.3)	7 (6.0)	35		
Great chance	20 (8.8)	12 (10.3)	32		
Any transactional sex in the last 3 months[a] (n=344)					
No	171 (75.3)	89 (76.1)	260	$\chi^2=0.0228$	0.880
Yes	56 (24.7)	28 (23.9)	84		
Alcohol use,>3 on AUDIT scale[b] (n=342)					
No	119 (52.0)	61 (54.0)	180	$\chi^2=0.1235$	0.725
Yes	110 (48.0)	52 (46.0)	162		
Drug use, In the past 3 months[c] (n=362)					

Table 1 (continued)

Background characteristics	Trajectory groups of TFV-DP levels in DBS			Test statistics Value	P value
	Consistently low (n = 248)	High decreasing (n = 120)	Total (n = 368)		
No	233 (96.3)	111 (92.5)	344	$\chi^2 = 2.4271$	0.119
Yes	9 (3.7)	9 (7.5)	18		
Depression symptoms (CES-D score ≥ 10)					
No	117 (47.2)	62 (51.7)	179	$\chi^2 = 0.6524$	0.41
Yes	131 (52.8)	58 (48.3)	189		
Intimate partner violence in the past year[f] (n = 355)					
No	122 (51.3)	61 (52.1)	183	$\chi^2 = 0.0241$	0.877
Yes	159 (48.7)	56 (47.9)	172		
Trajectories of attendance in adherence clubs					
Low slightly increased	89 (36.0)	30 (25.0)	119	$\chi^2 = 4.3809$	0.04
Consistently moderate	159 (64.1)	90 (75.0)	249		
Trajectories of response to SMS\ (n = 336)					
Consistently high	129 (58.1)	93 (81.6)	222	$\chi^2 = 18.5096$	< 0.001
Consistently low	93 (41.9)	21 (18.4)	114		
VOICE risk score, median (IQR)	7 (6–8)	7 (6–8)		H = 2.763	0.763
Social support[g] (n = 384), mean (SD)	3 (2–4)	3 (2–4)		H = 3.649	0.455
Stigma score[e] (n = 377), mean (SD)	10 (6–12)	9 (6–12)		H = 11.912	0.805

$\chi^2 \rightarrow$ Chi-square test, H → Kruskal–Wallis test

[a]Transactional sex is defined as having sex with a man because he provided her with or she expected he would provide her with food, clothes, cosmetics, items for children, transportation, cash, school fees, mobile phone, and other items

[b]An AUDIT-C scale score ≥ 3 was indicative of alcohol misuse

[c]Drugs include non-prescribed drugs (cannabis, cocaine, amphetamine-type stimulants, inhalants, sedatives, hallucinogens, opioids, and prescription drugs for nonprescription purposes, e.g., codeine)

[d]Center for Epidemiologic Studies-Depression (CES-D) scale, maximum score of 30; CES-D ≥ 10 was considered depressed

[e]Stigma was measured as the sum score across ten items assessing stigma related to HIV and PrEP use (range: 0 to 40)

[f]Participants were considered to have experienced any intimate partner violence if they answered "yes" that they had experienced at least one of four questions asking about physical, emotional, sexual violence, or feeling afraid, unsafe, or in danger from a sexual partner

[g]Social support was measured as the sum score across two items assessing social support from adults and close friends (range: 0 to 4)

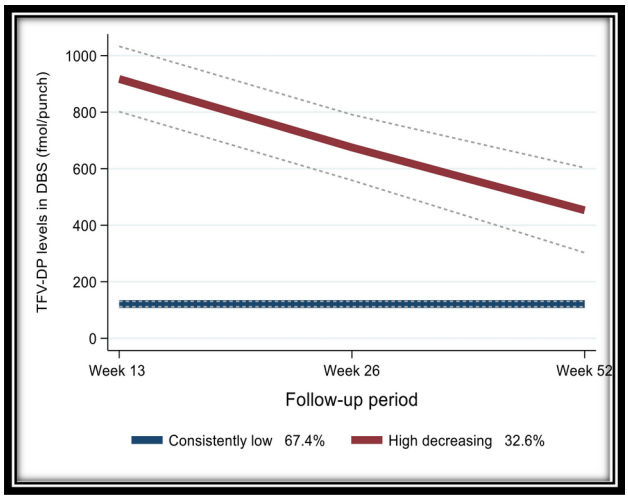


Fig. 1 Trajectories of TFV-DP levels in DBS

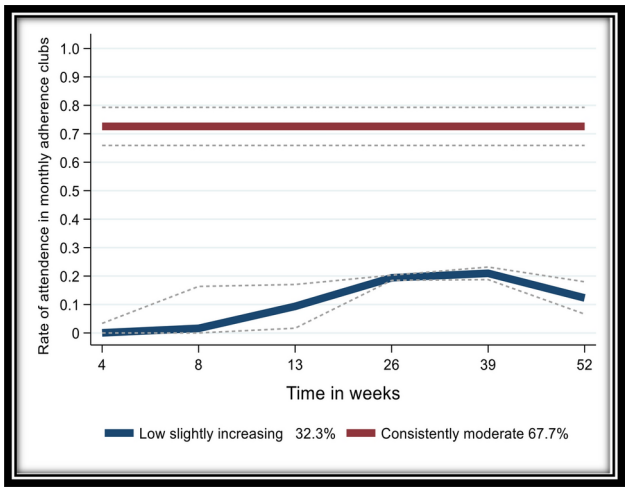


Fig. 2 Trajectories of voluntary attendance in monthly adherence clubs

CI 1.4–11.9; p = 0.010), compared to participants from Cape Town. Perceived HIV risk was also a significant factor.

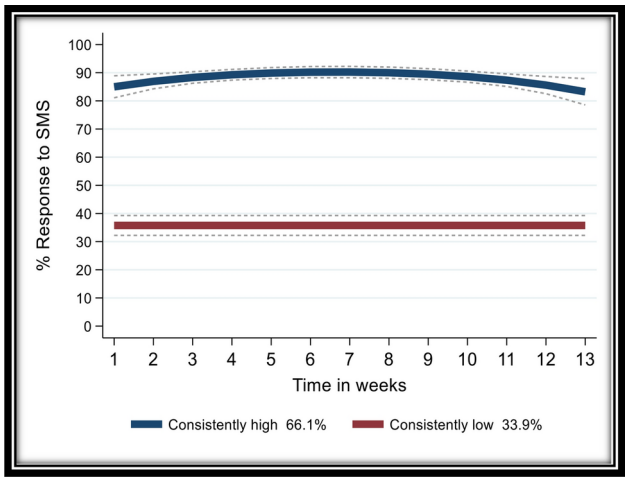


Fig. 3 Trajectories of responses to 2-way SMS

Participants who perceived a small chance of acquiring HIV in the next year had higher odds of adherence (AOR: 5.7; 95% CI 2.5–13.1; p < 0.001), and those who perceived a moderate chance also had increased odds of adherence (AOR: 3.8; 95% CI 1.1–13.5; p = 0.037). Women in the consistently high SMS response trajectory group had significantly higher odds of being in the high-decreasing TFV-DP levels trajectory group (AOR: 6.6; 95% CI 2.8–15.5; p < 0.001). In contrast, participants in the consistently moderate adherence club attendance trajectory group had an AOR of 1.3 (95% CI 0.5–3.3; p = 0.620), indicating no significant association between adherence club attendance and membership in the high-decreasing TFV-DP levels trajectory group.

Discussion

This analysis using GBTM of PrEP adherence demonstrates that higher engagement with weekly SMS was associated with the high but declining adherence trajectory. In this early study of oral PrEP uptake and adherence among South African and Zimbabwean AGYW, maintaining adherence remained a significant challenge. Only a minority of participants sustained high adherence over the 12-month study period, with 25.3%, 21.0%, and 8.0% having TFV-DP levels consistent with taking four pills per week at weeks 13, 26, and 52, respectively. GBTM identified two distinct adherence trajectories: a high-decreasing pattern (32.6%) and a consistently low pattern (67.4%). Women who responded to approximately 90% of weekly two-way SMS messages during the first three months of PrEP use had 6.6 times higher odds of being in the high-decreasing TFV-DP levels trajectory group compared to those with consistently low response rates. This association suggests a potential

Table 2 Determinants of membership in a high-decreasing TFV-DP levels trajectory

Background characteristics	Univariable analysis Crude OR (95%)	P value	Multivariable analysis Adjusted OR (95% CI)	P value
Study site				
Cape Town, South Africa	1.0	0.054	1.0	0.000
Harare, Zimbabwe	2.9 (1.7–5.1)		10.2 (3.5–29.2)	0.010
Johannesburg, South Africa	1.8 (1.0–3.1)		4.1 (1.4–11.9)	
Age groups				
<20 years	1.0	0.008	1.0	0.229
>=20 years	1.9 (1.1–3.2)		1.6 (0.7–3.5)	
Education				
College or university	1.0	0.017	1.0	0.174
Secondary school	1.7 (0.8–3.7)		2.2 (0.7–7.2)	0.067
Primary school	10.7 (1.8–62.2)		15.1 (0.8–274.2)	
Perceived risk of getting HIV in the next year (n = 344)				
No risk at all	1.0	0.019	1	<0.001
Small chance	2.2 (1.3–3.6)		5.7 (2.5–13.1)	0.037
Moderate chance	2.3 (1.02–5.4)		3.8 (1.1–13.5)	0.634
Great chance	1.8 (0.8–3.9)		1.4 (0.3–6.6)	
Primary partner's HIV status (n = 241)				
Don't know	1.0	0.096	1.0	0.510
HIV negative	0.6 (0.3–1.1)		0.8 (0.4–3.3)	0.417
HIV positive	0.6 (0.05–6.5)		0.3 (0.01–7.0)	
Trajectories of attendance in adherence clubs				
Low slightly increased	1	0.037	1	0.620
Consistently moderate	1.7 (1.03–2.7)		1.3 (0.5–3.3)	
Trajectories of response to SMS (n = 336)				
Consistently low	1	<0.001	1	<0.001
Consistently high	3.2 (1.9–5.4)		6.6 (2.8–15.5)	
Social support	1.3 (1.0–1.7)	0.048	1.2 (0.8–1.8)	0.453

Social support was measured as the sum score across two items assessing social support from adults and close friends (range: 0 to 4)

dose–response relationship between SMS engagement and PrEP adherence, warranting further investigation. Importantly, these interventions were chosen in part because they leveraged existing adherence support interventions already in use in these settings, making them more scalable.

A unique feature of this study was the application of GBTM to identify latent trajectories of TFV-DP levels and to characterize adherence support interventions as dynamic behaviors. Due to the differing measurement schedules across outcomes, we employed separate GBTM models for each outcome rather than group-based multi-trajectory modeling (GBMTM). The use of GBMTM would have required substantial data imputation, potentially introducing bias and limiting interpretability. Our objective was to identify distinct trajectories for each outcome and examine their independent associations with PrEP adherence, making separate models the more appropriate analytical approach. While GBMTM is a promising method for jointly modeling multiple outcomes, future studies with harmonized data collection schedules may explore its application to gain a more integrated understanding of the relationship between adherence trajectories and engagement with adherence support interventions.

GBTM has recently been applied in several studies to analyze PrEP adherence patterns among African women in South Africa [31, 32], East Africa (Kenya and Uganda) [33], and among transgender women in the United States [34]. As a data-driven approach, the number of adherence trajectories identified through GBTM depends on both sample size and the number of adherence measurement points over time. In contrast to the two trajectories identified in our analysis, Hurwitz et al. [31] and Pyra et al. [33] identified four trajectories using weekly adherence measurements collected via electronic monitoring systems. Consistent with our findings, Stoner et al. [32] identified two trajectories among 200 women—52% exhibited high early adherence that later declined, while 48% had persistently low adherence—using TFV-DP levels measured at five time data points. The decline in adherence among those with initially high levels, particularly after month three, may be linked to the transition from monthly to quarterly study visits. Similar adherence patterns have been observed in studies involving adolescents [35–38], suggesting that more frequent follow-up visits may help sustain adherence among initially motivated individuals. Multiple studies have also identified diverse factors contributing to adherence lapses and eventual discontinuation. De Vos et al. [39] highlighted how external challenges—such as school schedules, local mobility, and side effects—disrupt PrEP use, while social conflicts, including partner mistrust and stigma, further undermine adherence. Velloza et al. [40] emphasized that HIV-related stigma discourages both disclosure and adherence, as many young women fear being perceived as HIV-positive. Similarly, O'Rourke et al. [41] described the negative influence of social opposition—including stigma from partners and families, societal judgment, and competing life demands—on sustained PrEP use. Mudzingwa et al. [42] reported additional external barriers such as misconceptions, dependence on study-related benefits, and lack of partner or family support. They also describe behaviors like stockpiling or discarding PrEP in response to perceived low personal risk or community mistrust.

Attendance in adherence clubs has been shown to enhance self-efficacy and reduce social isolation [11]. Peer-led adherence support groups provide a valuable platform for discussing barriers to PrEP adherence, including side effects, stigma, and relationship challenges such as gender-based violence, while also facilitating strategies to address these barriers [33]. These groups also play a critical role in normalizing PrEP use, particularly in regions where PrEP has not yet been widely adopted, such as parts of Eastern and Southern Africa. A recent study of 247 HIV-negative AGYW using PrEP in South Africa, Uganda, and Zimbabwe found that in-person clubs and weekly phone calls were the most preferred adherence support strategies, followed by online clubs, additional counseling, and SMS [43]. In our analysis, we identified two latent trajectories of adherence club attendance. Most participants followed a consistently moderate trajectory, attending approximately 0.7 sessions per month (equivalent to two out of three club meetings every three months), suggesting good acceptability of the intervention. Although adherence club attendance was associated with PrEP adherence in the unadjusted analysis, no significant association was observed between adherence club trajectories and TFV-DP levels trajectories in the adjusted analysis. Women who discontinue PrEP may be less likely to continue attending adherence clubs, particularly in the absence of structured follow-up. Additionally, competing demands such as work and caregiving responsibilities may hinder attendance, highlighting the need for more flexible and accessible adherence support options. These could include digital interventions, such as WhatsApp peer-support groups [44], or integrating adherence support into routine healthcare visits.

Approximately two-thirds of AGYW consistently responded to at least 90% of the weekly two-way SMS messages during the first three months, indicating strong acceptability of SMS as an adherence support intervention. High SMS response rates may reflect the comprehensive adherence support offered in the trial setting, including ongoing counseling. Similarly, a recent study of 142 AGYW in Uganda found SMS reminders to be highly acceptable, with 90% of participants expressing willingness to receive them [45]. In our analysis, women with consistently high SMS

response rates had 6.6 times greater odds of belonging to the high-decreasing TFV-DP levels trajectory group compared to low responders. Supporting this finding, Pintye et al. [46] evaluated a PrEP-tailored, theory-based SMS support system among Kenyan AGYW and found that those enrolled after the SMS service was implemented were significantly more likely to continue PrEP than those enrolled before (43% vs. 22%; adjusted risk ratio = 1.75; p = 0.003). The SMS system also played a key role in enhancing participants' understanding of PrEP and addressing their concerns in real time. Our finding of a dose–response relationship between engagement with the weekly two-way SMS and adherence warrants further investigation.

PrEP is available as part of primary healthcare in South Africa and Zimbabwe, but its delivery remains largely facility-based. Lessons from community-based ART delivery in South Africa—where community clubs led to improved ART uptake, retention, and viral suppression compared to facility-based services—suggest that similar models could enhance PrEP access and adherence. While adherence clubs and SMS-based support remain largely limited to donor-funded programs, integrating adherence support and motivational counseling into existing initiatives, such as the Ideal Clinic program's youth-friendly services, may be a feasible approach. As efforts continue to expand differentiated PrEP service delivery in demedicalized settings, our findings may help inform future implementation strategies.

In this analysis, women who perceived a small or moderate risk of HIV acquisition demonstrated higher adherence, suggesting that a heightened sense of vulnerability may drive greater PrEP use. The effectiveness of PrEP depends on achieving high adherence during periods of elevated HIV exposure risk—a concept known as prevention-effective adherence [47]. A previous analysis of HPTN 082 data found that HIV risk factors such as condomless sex, multiple sexual partners, or having a primary partner living with HIV were associated with greater adherence within the same time interval, supporting the idea that AGYW can align PrEP use with periods of greater HIV exposure risk [48].

Our findings highlight potential strategies for improving oral PrEP adherence among African AGYW. First, adherence support interventions should be guided by objective indicators of PrEP use. Given the cost and limited availability of DBS assays for adherence monitoring, alternative objective tools should be explored to help providers identify PrEP users who may require additional support [49]. Novel point-of-care urine tenofovir lateral flow assays offer a qualitative indication of PrEP use in the prior week and could be used to tailor adherence counseling [50]. Weekly two-way SMS messaging may also support adherence by promoting regular engagement, offering personalized reminders, and enabling real-time communication to address medication-related concerns. This interactive approach can enhance accountability and encourage consistent PrEP use through ongoing patient-provider communication.

The strengths of this analysis include (1) the use of intracellular TFV-DP levels as an objective measure of cumulative PrEP adherence over 6–8 weeks, and (2) the application of GBTM to identify longitudinal trajectories of both TFV-DP levels and adherence support intervention engagement. However, several limitations should be noted. First, the HPTN 082 study was conducted between 2016 and 2018, when PrEP was a relatively novel intervention, and adherence declined substantially between week 13 and weeks 26 and 52. This limits our ability to examine the longer-term associations between SMS engagement, club attendance, and sustained adherence. Second, TFV-DP levels were measured at only three time points, with a large gap between the final two (week 26 and week 52), limiting the ability to capture more granular adherence trajectories. More frequent TFV-DP level measurements could provide clearer insights into adherence dynamics. Finally, self-reported data may be subject to social desirability and recall bias [51].

In conclusion, in this early PrEP demonstration study, adherence to PrEP was a challenge among South African and Zimbabwean AGYW. Encouragingly, a high response to two-way SMS was associated with higher adherence to PrEP. Providing acceptable PrEP adherence support interventions, such as two-way SMS, could improve PrEP adherence and enhance prevention effectiveness. Additional research is needed to develop adherence support interventions that improve oral PrEP adherence in this important population while simultaneously increasing access to longer-acting PrEP formulations. Furthermore, future research should incorporate qualitative assessments to better understand the barriers to implementing and optimizing adherence support interventions for adolescent girls, ensuring their effectiveness and sustainability in real-world settings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10461-025-04709-8.

Funding This work was supported by award numbers UM1-AI068619, UM1-AI068617, and UM1-AI068613, from the NIH (National Institute of Allergy and Infectious Diseases (NIAID)) to HPTN. This publication was made possible by Grant Number T32AI007433 from the National Institute of Allergy and Infectious Diseases. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declarations

Competing Interests No relevant financial or non-financial competing interests to report.

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