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The ATEAM study: Advances in technology to enhance PrEP adherence monitoring (ATEAM) among young men who have sex with men

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Abstract

Young age has consistently correlated with lower adherence to pre-exposure prophylaxis (PrEP) in young men who have sex with men (YMSM). Digital medicine, a dynamic healthcare platform of wearable physiological sensors and mobile communication technology that can respond to medication nonadherence rapidly, has the potential in promoting PrEP adherence. We evaluated the feasibility and acceptability of Proteus Discover, a digital monitoring adherence system, to measure PrEP adherence and provide real-time feedback among cisgender YMSM and transgender women. One hundred HIV-negative young men and transgender women ages 16–24 years were enrolled in a 24-week randomized controlled crossover study to tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) coencapsulated with Proteus Discover versus TDF/FTC standard-of-care. Participants in the 12-week Proteus Discover arm received weekly SMS text messages to promote pill taking based on Proteus Discover adherence data. Dried blood spots (DBS) were collected at 4-week intervals for tenofovir diphosphate (TFV-DP) in red blood cells as the referent and questionnaires were completed to assess acceptability, usability, and patterns of use. Linear mixed models analyzed the relationship between 30-day adherence measured by DBS and Proteus Discover. PrEP adherence was high overall. Adherence, as measured by DBS, was correlated with adherence as measured by Proteus Discover (*p* value = 0.03). Most participants reported that Proteus Discover helped them take their PrEP daily and that the system was easy to use. However, a majority (53.5%–60.5%) disagreed with the statement that wearing the patch was not an issue. There was an incremental increase in TFV-DP in DBS with adherence by Proteus Discover. More research is warranted to explore optimizing PrEP adherence for youth through real-time monitoring.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Lack of efficacy to pre-exposure prophylaxis (PrEP) is due almost exclusively to low drug adherence and the failure of traditional adherence metrics to precisely document drug adherence, identify patterns of adherence behaviors, and facilitate timely intervention when lapses in adherence occurred.

WHAT QUESTION DID THIS STUDY ADDRESS?
What is the feasibility and acceptability of Proteus Discover, a digital monitoring adherence system, to measure PrEP adherence and provide real-time feedback among cisgender young men who have sex with men (YMSM) and transgender women?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
This study successfully developed an integrated system that confirms ingestion of oral PrEP, monitors adherence both in real-time and longitudinally, and provides feedback mechanisms to promote enhanced adherence behaviors for YMSM.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
This study warrants further exploration in the use of digital medicine and real-time monitoring to optimize PrEP adherence for youth.

INTRODUCTION

Young men who have sex with men (YMSM) represent the greatest risk group for incident HIV transmission in the United States, accounting for 69% of all new infections.[1] National HIV surveillance data highlight the HIV treatment challenges among a majority of YMSM with 34% retained in care and started on antiretroviral therapy, and only 12% achieving viral suppression within 16 months of diagnosis.[2] Although great strides have been made to increase HIV prevention strategies, including risk reduction interventions, pre-exposure prophylaxis (PrEP), postexposure prophylaxis, adherence to HIV medication, linkage to, retention in, and re-engagement in care, these strategies have not met their full potential.[3]

Despite PrEP being identified as a high impact intervention for HIV prevention for YMSM, and being well known in the community with 85% of gay and bisexual men being aware of it, its potential impact has been underwhelming with only 25% of gay and bisexual men reporting that they have ever used it.[4] Further, the lack of efficacy to PrEP is due almost exclusively to low drug adherence and the failure of traditional adherence metrics to precisely document drug adherence, identify patterns of adherence behaviors, and facilitate timely intervention when lapses in adherence occurred.[5,6] In addition, young age has consistently correlated with lower adherence to PrEP, the dominant factor in PrEP effectiveness.[7-11]

Inadequate adherence, and the lack of tools that can reliably and rapidly intercept nonadherence, is a significant problem for the PrEP domain.[12-16] Digital medicine, a dynamic healthcare platform of wearable and implantable physiological sensors, mobile communication technology, and web-based communities in managing patient health, can respond to medication nonadherence rapidly with precise information to impact patient behavior toward favorable outcomes. Visual feedback is a program that enables a patient to visualize and monitor a real-time change of their disease activity parameters as well as reported outcome measures. With the emergence of activity trackers, wireless-enabled wearable devices that are synced to a computer and/or smartphone for long-term physiologic data monitoring, visual feedback messaging can be delivered in real-time in response to changes in health risk status.[17-19] Furthermore, text messaging has been shown to be an effective method of improving adherence to both treatment and prevention modalities.[20-24] Integrating a system that can triangulate wireless technology that (1) confirms medication ingestion with (2) a smartphone interface that captures temporal adherence patterns which can thereby trigger (3) real-time feedback of validated and population-specific HIV risk reduction education and health promotion through text messaging may offer a cohesive platform to optimize adherence to PrEP.

Proteus Discover was the first US Food and Drug Administration (FDA)-approved application of an integrated circuit sensor designed to directly measure drug ingestion events. PD consists of three interacting components: the ingestible sensor tablet, the adhesive personal

monitor (i.e., a patch), and the wireless communication network (i.e., a smartphone and central server). Once the sensor tablet coencapsulated with the drug is swallowed, it interacts with gastric fluids to generate a low frequency wave signal which is transmitted in real-time to the patch and registered as an ingestion event simultaneously to the smartphone device and central server. It has been shown to be effective in monitoring daily medication adherence with more than 99% accuracy in drug detection in patients with various chronic medical conditions, including cardiovascular disease, psychiatric illness, kidney transplant, and tuberculosis.[25–27] Our group was the first to establish bioequivalence for the coencapsulation of tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) with the Proteus ingestible sensor relative to unencapsulated native TDF/FTC as assessed by a rigorously conducted pharmacokinetic study.[28]

The purpose of the Advances in Technology to Enhance Adherence Monitoring (ATEAM) study was to evaluate a generalizable PrEP adherence monitoring approach among cisgender YMSM and transgender women who have sex with men to determine the feasibility as well as the acceptability of the Proteus Discover system to promote PrEP adherence and provide real-time feedback to modify adherence behaviors.

METHODS

The ATEAM was a 24-week randomized controlled trial utilizing a crossover design to monitor and promote adherence to daily oral TDF/FTC PrEP using Proteus Discover and weekly text messages. The crossover study design was implemented to leverage both intra- and interindividual observations of adherence patterns and preferences of each PrEP condition among all participants. We hypothesized that we may observe a carryover effect of longitudinal adherence persistence as the participants transition to the next 12-week condition. HIV-negative young men and transgender women aged 16–24 years, who were assigned male gender at birth, reported interest in PrEP, willing to use PrEP for at least 6 months, reported high sexual risk for HIV acquisition, and had no contraindications to TDF/FTC, the ingestible sensor, or topical adhesive previously, were eligible to join the study. Participants were recruited via clinical referrals, community partnerships, and various social media networking and dating platforms. No participants were using PrEP at the time they were enrolled in the study.

The study was approved by the Cook County Health Institutional Review Board (IRB) prior to the commencement of any study procedures. Written informed consent/assent was obtained from all participants prior to participation in the study. Participants under the age of 18 years were allowed to consent to study participation for themselves based on IRB approval and review of local laws. Once they consented, a baseline assessment was performed, including physical examination, HIV, sexually transmitted infections, and renal function screening laboratory tests, participants' demographics, beliefs about PrEP,[9] sexual history in the past 3 months, and in-depth analysis of the sexual behavior with last sexual partner. Participants were randomly assigned (1:1) using the Urn schema to either to the Initial Proteus (IP) arm where participants received Proteus Discover coencapulated with TDF/FTC for the first 12 weeks of PrEP and then crossed over to standard-of-care for PrEP with native TDF/FTC for the last 12 weeks, or the Crossover Proteus (CP) arm, where participants received standard-of-care for PrEP for the first 12 weeks and then crossed over to the Proteus Discover arm for the second 12 weeks of the study. As part of the enrollment process, participants were trained on how to use Proteus Discover and change the patch weekly, as well as educated on security procedures associated with the sensor system. All study participants were provided with TDF/FTC at no cost by the study.

Participants in the IP and CP arms were sent automated weekly text messages with information of estimated HIV risk reduction calculated from the sum of days of confirmed drug ingestion by Proteus Discover. There were three tiers of weekly text messaging, Tier 3/high adherence (4 or more doses per week), Tier 2/medium adherence (2–3 doses per week), and Tier 1/low adherence (1 or fewer doses per week). Tier 3 contained messages of praise for a job well done, the Tier 2 included messages of encouragement and support, and Tier 1 inquired how the participant was doing, reminded the participant that the research team was available for support, and requested a response. Dried blood spots (DBS) were collected at 4-week intervals for tenofovir-diphosphate (TFV-DP) in red blood cells as referent standard and computer-assisted self-interviews were completed at baseline, at the time of crossover to the next condition (week 12), and at the end of the study (week 24) to assess acceptability,[26] patterns of use,[29] rates of adherence,[30] product usability,[31] sexual risk, and beliefs about PrEP.[10]

Statistical analysis

Data on characteristics were summarized descriptively using frequencies for categorical measures, and means, SDs for continuous measures. The baseline characteristics of participants with complete and incomplete follow-ups of PrEP (week 12 for the IP arm and week 24 for the CP

arm) were further compared to evaluate the potential retention bias due to attrition. For continuous variables (e.g., age), the two groups are compared on the mean using a *t*-test. For categorical variables, the chi-square test is used to test for the difference between the two arms if the expected values of any category of a variable are greater than 5; otherwise, the Fisher exact test is applied. All analyses used two-sided tests for significance, with a statistical significance level of 0.05.

Linear mixed models that account for within-subject correlation among repeated measures were analyzed. The models investigated the relationship between 30-day adherence measured by DBS (TFV-DP measurement and DBS adherence) and Proteus Discover. The predictors were Proteus Discover adherence and week 4, 8, 12, 16, 20, and 24 DBS TFV-DP indicators with a random intercept for each participant.

For both of the two arms, at each timepoint, we compared the adherence measured by two different sources, DBS and Proteus Discover, using paired *t*-test. The reference standard used for this study is DBS which contains ~12 million RBCs per 3-mm punch and has been well-characterized to provide stable and consistent measures of cumulative drug exposure.[32] Based on directly observed dosing studies, participants can be categorized as four levels of adherence as follows: TFV-DP less than 349 fmol per punch (fewer than two tablets per week), 350–699 fmol per punch (two or three tablets per week), 700–1249 fmol per punch (four to six tablets per week), and 1250 fmol per punch or more (daily dosing).[33] The analysis considered the middle point for each level to translate the adherence level as the percentage of adherence to compare with the adherence levels measured by Proteus Discover and self-reported separately. Proteus adherence measurements were available when the participants were using Proteus Discover (i.e., weeks 4, 8, and 12 for the IP arm and weeks 16, 20, and 24 for the CP arm).

Only the eligible participants who were retained through follow-up study visits were considered when assessing acceptability. Two components were used to measure the acceptability, the acceptability assessment, and the system usability scale. Self-reported survey data on acceptability were summarized descriptively to access the usability of Proteus Discover and acceptability of the system components. The overall scores on a scale of 1–10 were considered as continuous scores in the following analysis. For categorical data, in order to have enough responses for each category and simplify the analysis, we collapsed the categories of responses together. The final categories considered were False/True, Disagree/Neutral/Agree, and Did not like it/Like. The IP arm and the CP arm were compared using the Fisher exact test and chi-square test for these categorical data with aforementioned conditions.

RESULTS

Demographics

Between November 2017 and April 2019, 100 HIV-negative YMSM ($n = 98$) and transgender women ($n = 2$) aged 16–24 years were recruited. A total of 100 participants were randomized equally into two groups, the IP arm and the CP arm. Table 1 summarizes the characteristics of participants at the baseline (week 0). The mean age of all participants was 21.9 years with the majority as male gender (97%), 33% Latinx, 28% White, 17% Black, and 22% Mixed. Around half of the participants had attended some college and one-third graduated from a tech school, college, or graduate school. The IP and CP groups were not statistically different from one another except for "ever been paid for sex" (28% in the CP arm vs. 8% in the IP arm, *p* value = 0.009).

Adherence with DBS and Proteus Discover

The measurements of Proteus Discover adherence were significantly smaller than the adherence measured by TFV-DP for all follow-up visits except week 4 for IP as presented in Table 2; participants might have taken some pills even if they did not wear the patch.

Mean PrEP adherence was high overall, more than four pills per week, as measured by TFV-DP levels, and there were no HIV seroconversions over the course of the study. For the linear mixed models, we only used the Proteus Discover data when the participants were wearing the patches. Each participant had a DBS test for each follow-up visit from week 4 to week 24. The adherence levels were defined as above. Because no participant took the study pill before the study, the TFV-DP measurement was considered as zero at the baseline for both of the two arms. Meanwhile, the adherence values measured by Proteus Discover were also recorded. Based on the linear mixed regression model of DBS adherence on Proteus Discover adherence as seen in Table 3, Proteus Discover adherence was positively related to DBS adherence, with a trend toward significance in the IP arm (*p* value = 0.20), and then significant for the CP arm (*p* value = 0.04).

Adherence was compared between the post-intervention period and intervention period in the CP arm. In the CP arm, in which Proteus Discover intervention was administered from 12 to 24 weeks, we expected to see a significant increase in adherence in the under-intervention compared to the pre-intervention period. The analyses here used the linear mixed effect model to account for within-participant correlation associated with repeated measures in response to the intervention over time, with

TABLE 1 Characteristics of participants at the baseline by two arms

	IP Arm (N = 50)	CP Arm (N = 50)	Total (N = 100)	p value
Age – mean (SD)	22.0 (1.89)	21.8 (2.11)	21.9 (2.00)	0.62[a]
Current gender – n				
Male	48 (96.0%)	49 (98.0%)	97 (97%)	1[b]
Transwoman/Transgender female	2 (4.0%)	1 (2.0%)	3 (3%)	
Race and ethnicity – n				
White	11 (22.0%)	17 (34.0%)	28 (28%)	0.08[c]
Black	9 (18.0%)	8 (16.0%)	17 (17%)	
Latinx	14 (28.0%)	19 (38.0%)	33 (33%)	
API, multiracial, and others	16 (32.0%)	6 (12.0%)	22 (22%)	
Identification – n				
Gay and queer	38 (70.0%)	42 (72.0%)	80 (80%)	0.32[c]
Bisexual, straight, and others	12 (20.0%)	8 (14.0%)	20 (20%)	
Education – n				
Eighth grade or less, more than eighth grade but did not complete high school, GED high school diploma	7 (14.0%)	8 (16.0%)	15 (15%)	0.83[c]
Some college	27 (54.0%)	24 (48.0%)	51 (51%)	
Tech school graduate and college graduate or higher	16 (32.0%)	18 (36.0%)	34 (34%)	
Working type – n				
No	11 (22.0%)	16 (32.0%)	27 (27%)	0.12[c]
Yes, full time	15 (30.0%)	20 (40.0%)	35 (35%)	
Yes, part-time	24 (48.0%)	14 (28.0%)	38 (38%)	
Living status now – N				
Your own house or apartment	28 (56.0%)	24 (48.0%)	52 (52%)	0.42[c]
Others	22 (26.0%)	26 (52.0%)	48 (48%)	
Been paid for sex – N				
No	46 (92.0%)	36 (72.0%)	82 (82%)	<0.01
Yes	4 (8.0%)	14 (28.0%)	18 (18%)	
Health insurance or coverage – N				
No or do not know	10 (20.0%)	10 (20.0%)	20 (20%)	1[c]
Yes	40 (80.0%)	40 (80.0%)	80 (80%)	

Abbreviations: API, Asian Pacific Islander; CP, Crossover Proteus; GED, General Educational Development; IP, Initial Proteus.

[a]*T*-test.

[b]Fisher exact test.

[c]Chi-square test.

an indicator for the period as the primary explanatory variable. The adherence in the under-intervention period significantly increased compared to the pre-intervention period by a coefficient of 0.05 with a *p* value of 0.03.

Figure 1 presents the visualization of text message tiers for both arms in the 12 consecutive weeks of using the Proteus Discover System. Patients in the IP arm had a higher weekly message tier (higher adherence) and 7-day adherence on average. However, patients in the IP and CP arms shared similar patterns in adherence, with participants having the lowest adherence in week 1

on Proteus Discover, adherence peaking in week 2, and then adherence gradually declining over the subsequent 10 weeks.

Feasibility and acceptability

Retention

There were 43 (86%) participants in the IP arm retained through the Proteus Discover follow-ups from baseline

TABLE 2 Comparison of adherence measured by TFV-DP and Proteus Discover at each time point

Arm	Week	Measurement in 30 Days	Mean (SD)	N	Paired t-test (p value)
IP (N = 50)	4	TFV-DP[a]	0.69 (0.27)	48	0.59
		Proteus	0.66 (0.29)	48	
	8	TFV-DP	0.75 (0.26)	43	<0.001
		Proteus	0.48 (0.30)	43	
	12	TFV-DP	0.73 (0.30)	40	<0.001
		Proteus	0.37 (0.28)	41	
CP (N = 50)	16	TFV-DP	0.77 (0.27)	38	<0.001
		Proteus	0.55 (0.30)	39	
	20	TFV-DP	0.78 (0.25)	35	<0.001
		Proteus	0.44 (0.32)	36	
	24	TFV-DP	0.70 (0.32)	38	<0.001
		Proteus	0.30 (0.30)	40	

Note: Analysis: only participants who completed both measurements are compared.

Abbreviations: CP, Crossover Proteus; IP, Initial Proteus; TFV-DP, tenofovir diphosphate.

[a]Week 4 TFV-DP concentrations are not at steady-state.

TABLE 3 Linear mixed regression of adherence measured by DBS on adherence measured by Proteus Discover with Proteus Discover data only collected with a patch

	Coefficient	SE	p value
IP Arm			
Intercept	0.51	0.16	<0.01
30-day adherence by Proteus Discover	0.22	0.17	0.20
Week 8 (yes/no)	0.09	0.03	<0.01
Week 12 (yes/no)	0.08	0.03	<0.01
CP Arm			
Intercept	0.46	0.16	<0.01
30-day adherence by Proteus Discover	0.36	0.17	0.04
Week 20 (yes/no)	0.02	0.04	0.63
Week 24 (yes/no)	0.02	0.04	0.55

Abbreviations: CP, Crossover Proteus; DBS, dried blood spots; IP, Initial Proteus.

to week 12, whereas 41 (82%) participants in the CP arm remained in the Proteus condition from week 12 to week 24.

Acceptability

Frequencies related to the acceptability assessment of the overall Proteus Discover were compared among IP versus CP (Table 4). The responses for each question have been collapsed into three categories. The majority of the participants in both arms agreed with most of the statements about acceptability assessment of the overall Proteus Discover, indicating that the system conferred a generally positive impact on both PrEP-specific behaviors and their overall health. However, only 30% of participants in the IP arm and 22% of people in the CP arm did not mind wearing a patch.

The majority of the users from both of the two arms felt that it was easy to learn and use the system consistently. However, there was a significant difference between the two arms about the opinions on whether the system was easy to use (p value = 0.04), well-integrated (p value = 0.03), and quick to learn (p < 0.001; see Table 5). The participants of the IP arm had a more positive attitude on Proteus Discover compared to that of the CP arm, which may reflect more favorable acceptance of new technology before personal routines and adaptations to study procedures are established.

We also examined acceptability based on the adherence levels indicated by TFV-DP drug level concentration. There was no difference between the two arms in the initial analysis, so we combined the two arms in the acceptability analysis (see Table 6). The four groups' mean scores were compared based on the analysis of variance (ANOVA) test. The belief in the prevention of HIV infection was significantly different between adherence groups. In the higher adherence level, the participants reported greater acceptability in taking pills, but there was no difference in the acceptability or usability of the Proteus Discover system itself. Meanwhile, people who only took no more than one pill per week did not think PrEP was good at preventing HIV infection.
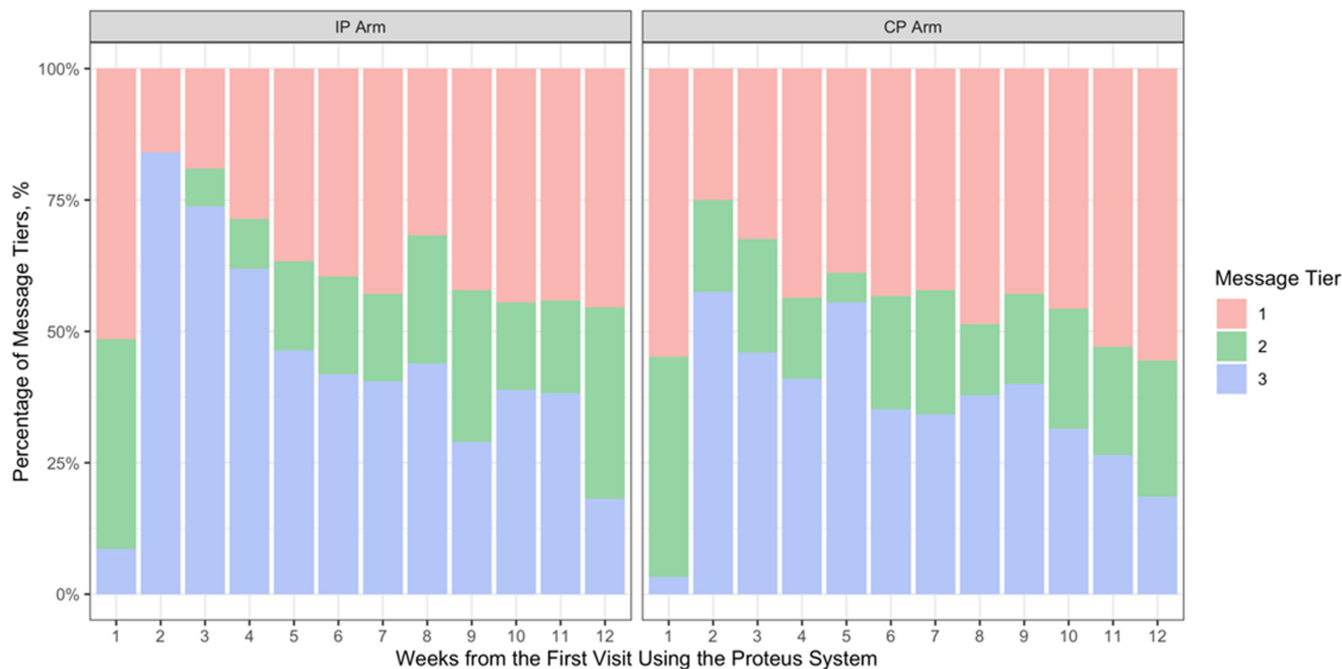
FIGURE 1 Percentage of participants by message tiers over the first 12 weeks of using the Proteus Discover system in the IP and CP arms (message tier 1: participants who took 0–1 pills in a given week would receive a text message inquiring how they were doing and a reminder that the research team was available if they needed additional support; message tier 2: participants who took two to three pills in a given week would receive text messages of encouragement and support; and message tier 3: participants who took four or more pills in a given week would receive text messages of praise for a good job). CP, Crossover Proteus; IP, Initial Proteus.

DISCUSSION

The current choices for real-time monitoring of adherence in both research trials and clinical settings have demonstrated flaws, and the evidence-base for PrEP adherence interventions is limited.[12,13] Results from our study provide evidence that real-time technology-based monitoring of PrEP coupled with real-time support is both feasible and acceptable for YMSM. Our technology-based monitoring and support system was able to provide useful real-time data that captured daily ingestion of PrEP, identify individual patterns of PrEP adherence, and advise real-time practice decisions for participants to modify adherence behaviors. The Proteus Discover in conjunction with weekly text check-ins did incrementally increase adherence as measured by DBS.

Most participants in both study arms found the Proteus Discover mobile phone app easy to learn and use and over half of the participants thought the Proteus Discover helped them take their PrEP daily and improved their experience of healthcare service for PrEP. The weekly text messaging data suggest participants were still acclimating to the system usability during the first week, with the wearable patch identified as a major barrier in full acceptance of the system among a majority of the PrEP users, with inconsistent patch application, particularly toward the final weeks of the respective 12-week intervention

in both arms, likely the source of lower measured adherence detected relative to protective DBS TFV-DP concentrations at each timepoint. The integrated weekly text messaging function was an important adjunctive monitoring feature to capture discordant patterns of pill taking between patch wearing and DBS concentrations that facilitated adherence in modifying behavior without further resource intensive interventions when participants were simply made aware of potential underperformance. Indeed, the majority of participants found that the overall Proteus Discover system coupled with real-time support enabled them to see how well they were managing their health and motivated them to improve their health, although less than half reported that the system assisted them in having more conversations with their healthcare providers.

Proteus Discover is the first integrated-circuit microsensor developed to confirm daily medication ingestion using a mobile device-based user interface to provide real-time continuous measurements of adherence and health-related activities. Prior to our study, the unique Proteus Discover System had been used exclusively for chronic diseases and has not been adapted for antiretroviral treatment or PrEP in the HIV field. Although the company has since filed for bankruptcy, use of this microsensor system has recently been replicated elsewhere.[34] More research is warranted to explore how best to optimize PrEP adherence

TABLE 4 Acceptability assessment of Proteus Discover by arms

Survey items	IP arm (N = 43, week 12) – N			CP Arm (N = 41, week 24) – N			p value
	Disagree	Neutral	Agree	Disagree	Neutral	Agree	
Easy to use Proteus in my daily routine	9 (20.9%)	9 (20.9%)	25 (58.1%)	10 (24.4%)	10 (24.4%)	21 (51.2%)	0.82[b]
Easy to learn how to use Proteus	0 (0.0%)	3 (7.0%)	40 (93.0%)	1 (2.4%)	6 (14.6%)	34 (82.9%)	0.23[a]
Showed me how well I am managing my health	6 (14.0%)	7 (16.3%)	30 (69.8%)	7 (17.1%)	8 (19.5%)	26 (63.4%)	0.83[b]
Motivated me to improve my health	8 (18.6%)	10 (23.3%)	25 (58.1%)	7 (17.1%)	7 (17.1%)	27 (65.9%)	0.73[b]
Helped me have more helpful conversations with my healthcare professionals	13 (30.2%)	13 (30.2%)	17 (39.5%)	11 (26.8%)	10 (24.4%)	20 (48.8%)	0.69[b]
Sharing my data with my healthcare professionals helped me understand my care plan	14 (32.6%)	11 (25.6%)	18 (41.9%)	12 (29.3%)	9 (22.0%)	20 (48.8%)	0.81[b]
Using Proteus improved my experience of healthcare service for PrEP	10 (23.3%)	9 (20.9%)	24 (55.8%)	9 (22.0%)	10 (24.4%)	22 (53.7%)	0.93[b]
Helped me see how I use PrEP from day to day	6 (14.0%)	4 (9.3%)	33 (76.7%)	4 (9.8%)	4 (9.8%)	33 (80.5%)	0.92[a]
Helped me take my PrEP more regularly	9 (20.9%)	6 (14.0%)	28 (65.1%)	10 (24.4%)	6 (14.6%)	25 (61.0%)	0.92[b]
Easy to use the iPad	2 (4.7%)	9 (20.9%)	32 (74.4%)	5 (12.2%)	11 (26.8%)	25 (61.0%)	0.32[a]
Easy to use the Proteus app	1 (2.3%)	7 (16.3%)	35 (81.4%)	10 (24.4%)	4 (9.8%)	27 (65.9%)	0.01[b,*]
Did not mind wearing the patch	26 (60.5%)	4 (9.3%)	13 (30.2%)	22 (53.7%)	10 (24.4%)	9 (22.0%)	0.17[b]
Connecting and applying each new patch was easy for me to do	9 (20.9%)	5 (11.6%)	29 (67.4%)	9 (22.0%)	9 (22.0%)	23 (56.1%)	0.41[b]

Abbreviations: CP, Crossover Proteus; IP, Initial Proteus; PrEP, pre-exposure prophylaxis.

[a]Fisher exact test.

[b]Chi-square test.

*$p < 0.05$.

through real-time monitoring and support platforms, particularly in promoting high user persistence beyond the first few weeks of utilization.

There are several limitations to our study. Our study size was limited to 100 participants, including only two transgender women, therefore we cannot generalize that our system would be both feasible and acceptable to transgendered people. Similarly, we did not separate our analysis by race/ethnicity, so we are unable to say there if there are differences in acceptability, usability, and feasibility by race/ethnicity. Exploring the social and cultural contexts among different race/ethnicity and minority groups in the future would enable us to fine-tune delivery and adherence strategies.[35] The majority (93%) of participants in our study viewed PrEP as a prevention tool that decreases their worry about acquiring HIV so their interest in both PrEP and use of our real-time support system may not be the same as other YMSM who do not regard PrEP as favorably. Unlike other studies that have used and assessed text messaging, we did not assess or evaluate the cost of

the overall system and whether it would be prohibitive for healthcare systems or patients to use.[12,35] Finally, the half-life of TFV-DP in plasma is ~2 weeks,[32] therefore the week 4 DBS measurements are ~75% of steady-state concentrations. The week 4 DBS mean concentration level is lower than at every subsequent timepoint, likely reflecting an underestimate of the expected adherence at week 4. However, as an underestimate of adherence, we avoid a potential type II error in our analysis.

CONCLUSION

If we have learned anything in the 40 years since the first HIV cases were first reported, it is that there is no one HIV prevention tool that is going to work for every population or community, we need multiple prevention tools to meet the needs of diverse populations. Although PrEP is an incredibly effective HIV prevention tool when used as directed, its biggest barrier in its effectiveness,

TABLE 5 Proteus discover usability scale by arms

Survey items	IP Arm (N = 43, week 12) – N			CP Arm (N = 41, week 24) – N			p value
	Disagree	Neutral	Agree	Disagree	Neutral	Agree	
Would like to use this system frequently	12 (27.9%)	10 (23.3%)	21 (48.8%)	11 (26.8%)	12 (29.3%)	18 (43.9%)	0.82[b]
Found the system unnecessarily complex	26 (60.5%)	7 (16.3%)	10 (23.3%)	23 (56.1%)	8 (19.5%)	10 (24.4%)	0.90[b]
System was easy to use	3 (7.0%)	4 (9.3%)	36 (83.7%)	6 (14.6%)	11 (26.8%)	24 (58.5%)	0.04[a]
Would need the support of a technical person to be able to use this system	33 (76.7%)	7 (16.3%)	3 (7.0%)	30 (73.2%)	6 (14.6%)	5 (12.2%)	0.76[a]
Found the various functions in this system were well integrated	4 (9.3%)	10 (23.3%)	29 (67.4%)	5 (12.2%)	20 (48.8%)	16 (39.0%)	0.03[a]
Thought there was too much inconsistency in this system	26 (60.5%)	12 (27.9%)	5 (11.6%)	22 (53.7%)	8 (19.5%)	11 (26.8%)	0.19[b]
Would imagine that most people would learn to use this system very quickly	4 (9.3%)	17 (39.5%)	22 (51.2%)	19 (46.3%)	10 (24.4%)	12 (29.3%)	<0.001[b]
Found this system very cumbersome to use	18 (41.9%)	16 (37.2%)	9 (20.9%)	20 (48.8%)	8 (19.5%)	13 (31.7%)	0.18[b]
Felt very confident using the system	1 (2.3%)	8 (18.6%)	34 (79.1%)	4 (9.8%)	13 (31.7%)	24 (58.5%)	0.12[a]
Needed to learn a lot of things before I could get going with this system	34 (79.1%)	4 (9.3%)	5 (11.6%)	34 (82.9%)	3 (7.3%)	4 (9.8%)	1.0[a]

Abbreviations: CP, Crossover Proteus; IP, Initial Proteus.

[a]Fisher exact test.

[b]Chi-square test.

TABLE 6 Mean scores for acceptability based on adherence levels by the end of using PrEP

Domains	0–1 pill/week (N = 10)	2–3 pills/week (N = 9)	4–6 pills/week (N = 26)	7 pills/week (N = 33)	ANOVA (p value)
How good do you think PrEP is at preventing HIV infection? (1–10) [beliefs about PrEP survey]	7.60 (2.41)	8.56 (0.53)	8.65 (0.94)	8.97 (0.68)	<0.05
How likely would you be to recommend Proteus to a friend who is interested in taking PrEP? (1–10) [acceptability survey]	7.10 (2.33)	7.67 (1.87)	7.92 (2.80)	6.70 (2.97)	0.38
Beliefs on PrEP (1, 2)	1.54 (0.16)	1.65 (0.08)	1.62 (0.21)	1.67 (0.17)	0.24
Acceptability assessment of Proteus (1–3)	2.25 (0.66)	2.42 (0.45)	2.54 (0.46)	2.38 (0.48)	0.39
Acceptability assessment of pills (1, 2)	1.52 (0.36)	1.89 (0.18)	1.82 (0.29)	1.87 (0.27)	<0.01
System usability (1–3)	2.41 (0.29)	2.50 (0.20)	2.59 (0.45)	2.44 (0.40)	0.44

Abbreviations: ANOVA, analysis of variance; PrEP, pre-exposure prophylaxis.

especially among young people, is not the drug itself, but low adherence. Obtaining adherence data in real-time and providing timely support can decrease prevention failure.[35–37] The ATEAM study successfully developed an integrated system that confirms ingestion of oral PrEP, monitors adherence both in real-time and longitudinally, and provides feedback mechanisms to promote enhanced adherence behaviors for YMSM. Our study represented the first introduction of Proteus

Discover for prevention of a disease state, a critical advance in assessing the first approved ingestible medication adherence monitoring program to avert a lifelong medical condition. Whereas this study examined the acceptability and feasibility of providing real-time support with real-time adherence monitoring among YMSM, this system could also be utilized among other adolescent populations and other high-risk populations that struggle with PrEP adherence.

AUTHOR CONTRIBUTIONS

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