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DigiPrEP: A Pilot Trial to Evaluate the Feasibility, Acceptability, and Accuracy of a Digital Pill System to Measure PrEP Adherence in Men Who Have Sex With Men Who Use Substances

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Background: Adherence to once daily oral preexposure prophylaxis (PrEP) for HIV prevention can be challenging for men who have sex with men (MSM) with substance use. Digital pill systems (DPS) comprise a radiofrequency emitter integrated into a gelatin capsule containing PrEP, which transmits data to a wearable Reader following ingestion, thereby enabling direct, real-time adherence measurement. This study evaluated the feasibility, acceptability, and accuracy of a DPS to measure PrEP adherence.

Methods: A 90-day, single-arm, open-label, pilot demonstration trial was conducted with adult, cisgender, HIV-negative MSM on PrEP with nonalcohol substance use. Feasibility was measured via DPS engagement and timeline followback. Acceptability was assessed via qualitative user experience interviews. Accuracy was evaluated via DPS performance metrics, pill counts, and DBS to quantify tenofovir diphosphate.

Results: Sixteen MSM enrolled (median age, 32 years), and 15 completed the study. Engagement remained stable over time. Emergent nonadherence patterns included intercurrent substance use. The DPS was largely acceptable based on interviews; the predominant barrier to use was the Reader. DPS-recorded ingestions totaled 1099, including 83.9% were detected by Reader and 16.1% were reported manually. The DPS recorded 92.2% of 1192 total expected ingestions per pill counts. Point-biserial correlation (R = 0.58; 95% CI: 0.21 to 0.80; $P = 0.047$) and Pearson correlation (month 1: R = 0.85; 95% CI: 0.57 to 0.95; $P = 0.0002$; month 3: R = 0.75; 95% CI: 0.17 to 0.94; $P = 0.0197$) showed strong correlations between DPS-recorded adherence and tenofovir diphosphate in dried blood spots.

Conclusion: DPS are a feasible, acceptable, and accurate method of measuring PrEP adherence in MSM with substance use. Future investigations should incorporate DPS into behavioral interventions targeting nonadherence.

Key Words: digital pill system, ingestible sensors, PrEP, HIV prevention, adherence

(*J Acquir Immune Defic Syndr* 2022;89:e5–e15)

INTRODUCTION

In 2010, the multinational iPrEX trial demonstrated that once daily tenofovir disoproxil fumarate/emtricitabine (TDF-FTC) as preexposure prophylaxis (PrEP) was 99% efficacious for preventing HIV in men who have sex with men (MSM).[1,2]

Received for publication July 15, 2021; accepted October 21, 2021.

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P. R. Chai is funded by NIH K23DA044874, R44DA051106 and research funding from Gilead Sciences (ISR-17-1018), Hans and Mavis Psychosocial Foundation and e-ink corporation, K. H. Mayer and C. O'Cleirigh are funded by NIAID P30AI060354, E. W. Boyer and R. K. Rosen are funded by NIH R01DA047236. J. Castillo-Mancilla is funded by NIAID R01AI145453.

The authors declare no conflicts of interest.

Parts of these data were previously presented at the Adherence 2020 Virtual conference sponsored by the International Association of Providers of AIDS Care (IAPAC); November 2–3, 2020; Orlando, FL.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Trial Registration: ClinicalTrials.gov identifier: NCT03842436.

Protection of Human Subjects: All study procedures were conducted in accordance with the ethical standards of the Fenway Health Institutional Review Board and with the Helsinki Declaration of 1975, as revised in 2000.

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Subsequent clinical trials and real-world demonstration projects have confirmed the efficacy of PrEP. Yet, adherence remains variable for many, especially those with concomitant substance use, who may benefit most from PrEP. As the rollout and acceptance of PrEP in the United States continues to increase, it is important to measure and support adherence among those using PrEP.[3,4]

PrEP adherence is challenging in the presence of mental health, substance use, or high-risk events like condomless sex.[5] For MSM with substance use, these barriers to PrEP adherence can lead to suboptimal adherence at critical junctures in HIV prevention.[6,7] Techniques to measure adherence patterns may detect early changes in PrEP-taking behavior, which can be used to address barriers to adherence.

Many tools exist to measure adherence, including indirect measures like self-report, pill counts, and electronic adherence monitors, in addition to direct measures like ingestible sensors, video-based observed therapy, and pharmacologic assays to measure drug concentrations.[8–10] Although each of these strategies seeks to confirm adherence and nonadherence, digital pill systems (DPS) enable the direct measurement of medication ingestion events in real time. Therefore, the advantage of such systems is their ability not only to verify adherence events and patterns in general but also to provide important information surrounding the specific contexts that may lead to suboptimal and frank nonadherence. Understanding adherence patterns through DPS technology can also allow for the development of behavioral interventions that leverage real-time adherence data, including information about the context in which it occurs, to provide relevant interventions at opportune moments to reinforce adherence.[11]

In a DPS, a capsule shell with an integrated radiofrequency sensor overencapsulates PrEP to form a digital pill. The digital pill transmits ingestion data via a radiofrequency signal to a wearable Reader device, which then relays the data to a smartphone app and dashboard, thereby enabling real-time, direct measurement and contextualization of PrEP adherence. DPS, which have received clearance from the US Food and Drug Administration, have been deployed in real-world settings to measure adherence to antidiabetics, antihypertensives, heart failure therapies, opioids for pain management, transplant medications, and antiretroviral agents.[12,13]

Our previous qualitative work explored the perceptions and potential acceptance of the DPS for measuring PrEP adherence among prospective DPS users; participants were HIV-negative MSM with nonalcohol substance use. Participants were accepting of the technology overall and perceived access to a real-time record of their PrEP ingestions to be among the most helpful components of the DPS.[14] To assess the feasibility, acceptability, and accuracy of deploying a DPS to measure PrEP adherence among real-world DPS users, we conducted a single-arm, open-label, pilot demonstration trial with the same population involving 90 days of DPS use with PrEP. The primary outcome of interest was the feasibility of the DPS; secondary outcomes included the acceptability and accuracy of the technology.

METHODS

Participants and Setting

Sixteen participants were enrolled in the pilot trial (NCT03842436). The sample size was determined based on previous feasibility studies using digital pills in the context of other medications and disease states (eg, opioid adherence in acute pain patients).[15] The inclusion criteria were as follows: (1) 18 years or older; (2) cisgender MSM; (3) self-reported substance use other than alcohol in the past 6 months; (4) maintained on once daily TDF-FTC as PrEP; and (5) had qualifying laboratory tests for PrEP [ie, negative rapid HIV test, creatinine clearance $\geq$60 mL/min, prior hepatitis B immunization, screening for sexually transmitted infections (STIs)]. Exclusion criteria included were as follows: (1) non-English speaking; (2) living with HIV per self-report; (3) transgender; (4) estimated creatinine clearance of $<$60 mL/min; (5) receiving active hepatitis B treatment; (6) taking proton pump inhibitors; (7) history of Crohn disease or ulcerative colitis; (8) history of bowel surgery, gastric bypass, or bowel stricture; (9) history of gastrointestinal malignancy or radiation to the abdomen; (10) not owning a smartphone; or (11) being unable or unwilling to ingest the digital pill.

All study procedures were conducted at Fenway Community Health, a health center and research institute in the greater Boston area focused on lesbian, gay, bisexual, transgender and queer or questioning health research, training, education, policy, and advocacy. This investigation was approved by the Fenway Community Health Institutional Review Board and was conducted between March 2019 and April 2020.

Digital Pill System

We used a novel DPS, the ID-Cap System (etectRx, Gainesville, FL) to directly measure PrEP adherence (Fig. 1).[12,16,17] This system comprises the following: (1) an ingestible radiofrequency emitter, coupled with a standard size 000 gelatin capsule (9.91 mm $\times$ 12.95 mm $\times$ 0.112 mm; Qualicaps Whitsett, NC[18]), which overencapsulates TDF/FTC as PrEP to create a digital pill; (2) a Reader device, which receives and transmits ingestion data from the digital pill; and (3) a smartphone app that displays adherence information to participants and transmits data to the study team. Upon ingestion, the digital pill is activated by chloride ions in gastric fluid and emits a radiofrequency signal, which is acquired by the wearable Reader. The Reader stores and forwards ingestion data using low-energy Bluetooth (BLE) to a participant-facing smartphone app and an online clinician dashboard, which facilitates on-demand visualization of adherence data by patients and clinicians.[17]

Following a successful ingestion using the DPS (ie, oral ingestion of a digital pill and correct operation of the Reader), an in-app notification reading "Ingestion detected" was sent to the participant's smartphone. Participants could also manually record ingestion events via the app. They were instructed to do so only if they ingested a digital pill but were unable to use the Reader or to confirm an ingestion with the use of the Reader (eg, digital pill not detected by the Reader or ingestion event not displayed in the smartphone app).[19]

FIGURE 1. Overview of DPS. The DPS includes an ingestible sensor within a gelatin capsule that overencapsulates a medication. When ingested, it is activated by gastric fluid, broadcasting a radiofrequency signal that is acquired by a wearable Reader device and relayed to a smartphone, which can display and transmit real-time adherence metrics. Image courtesy of etectRx.

Procedures

Recruitment and Prescreening

Recruitment methods included community and social media outreach throughout the greater Boston area. Potential participants were prescreened; those who met preliminary eligibility criteria were invited to attend an in-person screening visit.

Study Visits

Potential participants were screened to confirm eligibility. Eligible participants then completed an in-person

quantitative assessment and received training on DPS operation.[19] Following the training session, the DPS and a 30-day supply of digital PrEP pills were provided. Participants demonstrated competence with the DPS by ingesting their first digital pill under direct observation and were instructed to take PrEP once daily thereafter. Participants returned for 3 study visits at months 1, 2, and 3. Thirty-day refills of digital pills were dispensed at months 1 and 2, and manual pill counts of unused digital pills from the prior month were conducted at all visits. Timeline followback assessments were also conducted at each visit. Finally, at month 3, participants completed an individual qualitative interview exploring their experiences with operating the DPS.

Measures and Analyses

Quantitative Assessment

Participants self-reported information on sociodemographics, PrEP status, missed PrEP doses during the past 2 weeks, STI history, sexual history, and substance use history. Data were stored and managed in the Research Electronic Data Capture system.[20] Descriptive statistics were calculated for selected quantitative variables.

Primary Outcome: Feasibility

Engagement With the DPS

The feasibility of the DPS was assessed via an examination of participant engagement with the technology, while taking once daily PrEP, over the 90-day study period. Engagement with the DPS was then measured by calculating the number of DPS-recorded ingestions (including both Reader-detected and manually reported ingestions) across each month, as well as the total number of DPS-recorded ingestions across the entire study period, and comparing those with the number of expected PrEP ingestions based on pill counts. We calculated mean ingestions at months 1 and 3 and evaluated the significance of the difference in the means using a matched-pair t test. We additionally calculated a Pearson correlation between overall DPS-recorded ingestions and pill counts. For the differences in means and correlation, we eliminated 1 participant who did not complete month 3 of the study.

Contextual Basis of Nonadherence

Timeline followback assessments were conducted at each monthly visit to evaluate temporal and contextual patterns of adherence and nonadherence as a component of DPS feasibility. During each timeline followback assessment, participants were presented with their PrEP adherence data from the previous month, as recorded by the DPS, and asked to report on the context of each nonadherence event. Contemporaneous notes from these assessments were then examined by the study team, and specific patterns (eg, weekend nonadherence, ingestions at particular times of day) were extracted.

Secondary Outcome: Acceptability

Qualitative User Experience

Acceptability was evaluated via individual, qualitative, user experience interviews conducted at the end of the 90-day study period. The interview guide was grounded in the Technology Acceptance Model and was developed by the study team (P.R.C. and R.K.R.) and piloted among study staff (P.R.C., Y.M., G.R.G., and M.J.B.).[21] Questions explored participants' experiences using the DPS, including facilitators and barriers to use, engagement with the technology, and willingness to use the DPS long term. The design, administration, and analyses of these interviews were conducted in accordance with the Consolidated Criteria for Reporting Qualitative Research guidelines.[22]

Qualitative user experience interviews were transcribed and coded using applied thematic analysis.[23,24] Three trained study team members (G.R.G., Y.M., and J.N.) generated the codebook. All interviews were then double coded by 2 study team members (A.B. and O.B.); coding was paused and evaluated every 5 transcripts to ensure consistency and to resolve and document any discrepancies. A kappa statistic was calculated, using a cutoff of >0.8 to ensure interrater reliability between coders. Coders reviewed aggregate coding to identify and discuss final themes surrounding user experiences, which were reviewed by the study team as a whole. Qualitative analyses were facilitated by NVivo software.[25]

Secondary Outcome: Accuracy

DPS Performance

Multiple DPS performance metrics were used to measure the accuracy of the DPS for detecting PrEP ingestions. The ground truth of PrEP ingestion events was defined as the pill counts conducted each month (ie, the number of unused pills returned, subtracted from the number of pills previously dispensed). The number of DPS-recorded ingestions—which included the number of both Reader-detected and manually reported ingestions—was compared with the aggregate pill count at each monthly time point; this was defined as the overall performance metric for the DPS. The Reader-detected ingestions count was used to reflect the number of times the DPS was operated correctly. Successful DPS operation was defined as ingestion of a digital pill, proper use of the wearable Reader, and confirmation of the ingestion on both the Reader and the app. Internal device metrics from the Readers—including accelerometer data, which indicated whether the Reader was moved, charged, and had contextual patterns consistent with moving and placing the Reader over the neck in proximity to a manually reported ingestion—were used to validate whether manually reported ingestions were caused by technical issues with the DPS or nonadherence to the technology.

Pill Counts

Monthly pill counts were conducted at all study visits; the number of unused pills returned from the 30-day supply dispensed at the previous month's visit was used to calculate the expected number of total PrEP ingestions per month. Pill

counts served as a comparison with day-to-day adherence measured by the DPS and were used as 1 ground truth measure of adherence that allowed us to better characterize DPS performance.[10]

Correlation of Tenofovir Diphosphate in Dried Blood Spot With DPS Adherence

The accuracy of the DPS was also measured by correlating drug concentrations of tenofovir diphosphate (TFV-DP) from dried blood spot (DBS) samples to DPS-recorded adherence. Together with pill counts, DBS samples were used as a second ground truth measure to compare with longer term adherence measured by the DPS.[10] Blood for DBS samples was collected at the end of months 1 and 3. We conducted phlebotomy and collected 5 mL of peripheral venous blood from participants into an EDTA anticoagulated sample collection tube. A micropipette was used to spot approximately 100 μL of fresh whole blood onto a Whatman 903 protein saver card. Cards were dried at room temperature for up to 8 hours and stored at −80°C until the assay date. Postdose collection time was not recorded; however, given the 17-day half-life of TFV-DP in DBS, the impact of a single dose of TDF-FTC on the DBS-derived concentration of TFV-DP is minimal.[9,26] Liquid chromatography/mass spectroscopy was used to quantify TFV-DP concentrations using previously described protocols.[27] DBS were punched twice per spot using a disposable 3-mm puncher and assayed using liquid chromatography–mass spectroscopy (LC/MS). Each DBS sample was injected into the LC/MS system 5 times and processed in duplicate to account for intraassay and intraday variation.

Drug concentrations of TFV-DP, as measured in DBS at months 1 and 3, were compared with DPS-recorded PrEP adherence. First, all DBS samples that were obtained more than 5 days after the conclusion of DPS-recorded ingestions (eg, as a result of scheduling challenges) were identified and excluded from analysis, as they resulted in incomplete data to compare with DPS-recorded ingestions. All other DBS samples were paired, based on their collection dates, with the corresponding average of DPS-detected ingestions during the 3-week period before DBS collection. We dichotomized TFV-DP levels using a cutoff of ≥700 fmol/punch based on existing data, demonstrating that a concentration of 700 fmol/punch is associated with at least 4 doses of PrEP ingested per week.[26,28] Using TFV-DP in DBS <700 vs ≥700 fmol/punch as a dichotomous variable, and considering the granular continuous adherence data from the digital pill, we then calculated a point biserial correlation between TFV-DP in DBS and digital pill adherence. Finally, we analyzed the paired TFV-DP concentrations and DPS-recorded adherence data at months 1 and 3 and calculated Pearson correlation coefficients for each independent time point. Analyses were completed using SAS (version 9.4).[29]

RESULTS

During the study period, 42 individuals were prescreened; of whom, 9 were ineligible and 16 declined to participate; reasons are provided in Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B757. Seventeen individuals attended a screening visit, and 16 were eligible and enrolled. Two individuals were originally deemed lost to follow-up, 1 of whom ultimately reengaged in the study approximately 5 months after being deemed lost to follow-up; this individual completed a qualitative interview but did not resume the use of DPS. Therefore, 15 participants completed the study, including follow-up assessments (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B757).

Among the 15 completers, all participants identified as cisgender MSM with a median age of 32 years (range, 24–49 years). Participants were primarily white (67%) and non-Hispanic (73%) (Table 1). Fourteen were on PrEP at the time of enrollment (93%); of these, 2 reported 1 or 2 missed doses in the prior 2 weeks (14%), 1 reported 5 or more missed doses (7%), and 11 reported no missed doses (79%). Ten participants reported acquiring a STI in the previous 12 months (67%). Alcohol use was the most frequently reported substance among participants (93%), followed by marijuana (67%), stimulants (47%), poppers/amyl nitrate (47%), and hallucinogens (27%).

Feasibility

Engagement With the DPS

Participants' engagement with the DPS over the 90-day study period is displayed in Figure 2 (panel A). The number of monthly DPS-recorded ingestions declined over the course of the study (month 1: n = 411, month 2: n = 368, month 3: n = 320). Over the course of the study period, the DPS detected a mean adherence of 75 (95% CI: 64.6 to 86; SD: 19) of 90 ingestions, whereas pill counts detected a mean of 82 injestions (95% CI: 77.5 to 86.7; SD: 8). When comparing adherence at months 1 and 3, participants ingested a mean of 28 pills (95% CI: 27 to 29.6; SD: 2) in month 1, versus a mean of 23 pills (95% CI: 18 to 28; SD: 8.7) in month 3 with a mean difference of 5.4 (95% CI: 0.65 to 10; SD: 8.6; $P = 0.014$), suggesting that there was a statistically significant decrease in PrEP adherence from month 1 to 3. Although some participants experienced a decrease in DPS-recorded ingestions as the study period progressed, this decrease may have been a result of nonadherence to PrEP, rather than nonadherence to the DPS (Fig. 2, panel B).

Acceptability

Qualitative User Experience

Qualitative user experience interviews yielded key themes surrounding the overall acceptability of the DPS, operational insights about its use, barriers to use, engagement, and willingness to use the technology long term (Table 2). This study focuses primarily on the overall usability of the DPS and barriers to use; a more detailed exploration of qualitative themes is reported elsewhere. Most participants reported that the DPS was easy to learn and did not interfere with their daily routines. The majority of participants' routines included first placing the Reader device over their

TABLE 1. Sociodemographics of Study Completers

Variable	Sample (n = 15) n	%
Age (in yrs)		
Median (interquartile range)	32 (6.5)	—
Range	24–49	—
Race		
White	10	67
Black	1	7
Asian	1	7
More than 1 race	2	13
Other	1	7
Ethnicity		
Not Hispanic or Latino	11	73
Hispanic or Latino	4	27
Education		
Some college	2	13
College degree	7	47
Graduate degree/professional	6	40
Sexual orientation		
Homosexual or gay	13	87
Bisexual	2	13
Relationship status		
Single	10	67
Domestic partnership	2	13
Married	2	13
Separated	1	7
Ever had an STI		
Yes	10	67
No	5	33
STIs in prior 12 mo		
Chlamydia	2	13
Gonorrhea	3	20
Syphilis	1	7
None	11	73
Sexual partners in past 3 mo		
Median (interquartile range)	5 (8)	—
Range	1–30	—
Condom use in past 30 d		
Never	4	27
Almost never	2	13
Sometimes	1	7
Almost every time	4	27
Every time	3	20
Not applicable	1	7
Times used stimulants before or during sex in past 3 mo		
Mean (SD)	5.7 (17.2)	—
Reported substance use		
Alcohol	14	93
Marijuana	10	67
Stimulants	7	47
Hallucinogens	4	27
Other (poppers, amyl nitrate)	7	47
Currently prescribed PrEP		
Yes	14	93
No	1	7
Nonadherent to PrEP in prior 2 wk (self-report)*		
Yes	3	21
No	11	79
Type of smartphone owned		
Apple	9	60
Android	6	40

*Defined as missing >2 doses of PrEP over the past 2 weeks. The denominator for this variable is 14, as 14 participants had already been prescribed PrEP, and 1 had not.

neck, opening the app on their smartphone, and then ingesting the digital PrEP pill. They reported going about their daily routines and then removing the Reader and placing it back on the charger, only after receiving a confirmatory message indicating that the ingestion had been detected (Fig. 3).

Some participants reported using the app linked to the DPS to access their own PrEP ingestion history throughout the study period. The primary reason for doing so was concern that they had forgotten a dose; in these instances, the app provided a repository of accessible information that confirmed prior ingestion events, which afforded participants ease of mind around and confirmation of their adherence (or nonadherence). Participants identified the ability to visualize their own historical PrEP ingestion data in an on-demand fashion as a facilitator to engaging with the DPS.

The predominant barrier to DPS use was the Reader. In most instances where participants did not successfully operate the DPS, this was to the result of forgetting to charge the Reader or not wearing the Reader around the neck during ingestions. The Reader was described as cumbersome when traveling or away from home, but it did not cause participants to disengage from DPS use throughout the study. Despite these barriers, most participants reported that the technology was easy to operate overall, and that they would be willing to engage with the DPS over the long term for the purposes of ongoing PrEP adherence measurement.

Accuracy

DPS Performance and Pill Counts

A total of 1099 DPS-recorded ingestions (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B757) occurred across all participants. Of these, 84% (n = 922) were Reader detected and 16% (n = 177) were manually reported. Reader-detected ingestions and manually reported ingestions that co-occurred within 30 minutes were identified and reconciled, as such events likely represented episodes in which a digital pill was ingested, and the ingestion was detected by the Reader, but the participant elected to manually record the ingestion in-app because the Reader was not correctly paired to the smartphone or was delayed in detecting the ingestion.

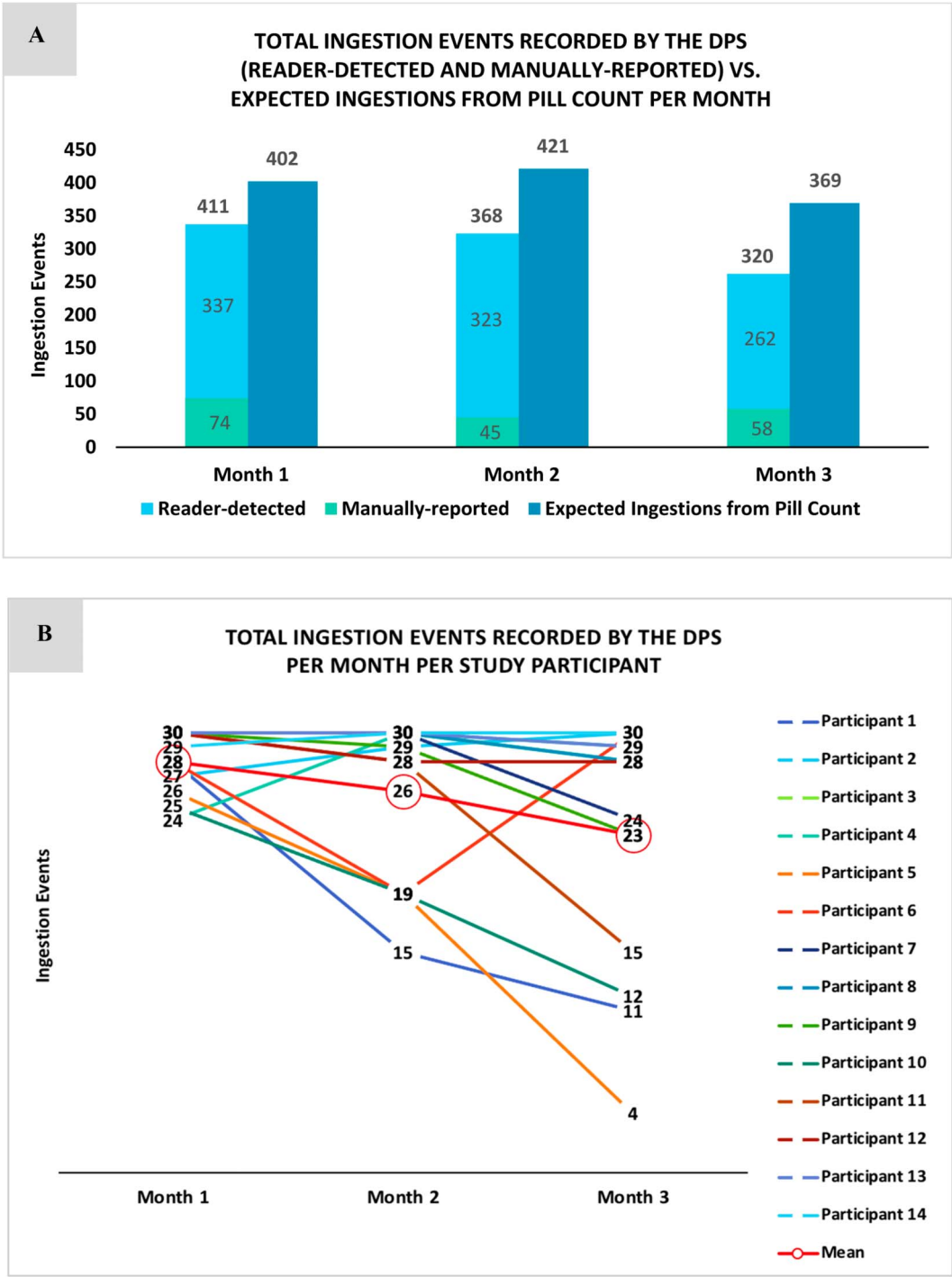

FIGURE 2. Engagement with DPS over the 90-day study period. Engagement with the DPS was consistent over the 90-day study period. Although the number of DPS-recorded ingestions decreased from month 2–3, this was paralleled by a decrease in PrEP adherence from month 2–3 (A). Individual-level engagement with the DPS was high with most participants (B). The participant who was temporarily lost to follow-up was excluded from the above graph; therefore, only 14 participants are included.

A total of 1192 potential PrEP ingestions, based on pill counts, were counted as ground truth, and DPS-recorded ingestions accounted for 92% (95% CI: 91 to 94) of all expected ingestions. We first calculated the number of successful operations of the DPS, which were defined as ingestion of a digital pill, proper use of the Reader for ingestion detection, and confirmation of ingestion on both the Reader and app. Excluding instances in which the manual recording feature was used, the proportion of successful DPS operations (n = 922) compared with overall total ingestion

TABLE 2. Representative Quotes From Qualitative User Experience Interviews

Themes	Quotes
Overall experience using the DPS	*I think the digital pill is pretty awesome to be able to track when you're taking PrEP. You have a record of when you've taken it, cause when I take it without the machine, sometimes I wonder whether or not I've taken it, so it's good to kinda keep track for my records when I've taken it and what time I've taken it.* – Age 28
Barriers to DPS adoption	*I found one thing that could be a little bit annoying is that if the device Reader was far away from the phone… the only time when I ever felt like, "Oh, this is a pain," or, "This is something I wish were easier," is when I would have to go and get my phone, and bring it to the kitchen by the pill, and then go and get the Reader, and get the Reader, and bring the Reader to the kitchen, but that only happened a few times, cause usually I have my phone in my pocket.* – Age 29
Engagement with the DPS	*Frequently, I wouldn't be looking at the [Reader indicator light] color. I'd be browsing my phone, and I'd get the [confirmation message] pop up on my phone. I'd be like, "All right, cool. I'm done. I can take this off now." I was completely okay with that. That's a good bookend to know that I've completed the procedure, so that's completely fine for me. It's not like it's spam. I know I'm taking those actions, so seeing that pop up is an affirmative thing for me.* – Age 32
Willingness to use the DPS after study	*I think that this is something that I'd recommend to others and that I like to actually tell my friends about, because I think it's how we can build awareness, and I think there's a lot of cool ways where we can use this technology for PrEP for lots of different populations that need help with that adherence, and just the general public.* – Age 33

events based on pill counts (n = 1192) demonstrated that the DPS successfully recorded PrEP ingestions 77% of the time. The accuracy of the DPS in detecting adherence remained consistent across months 1, 2, and 3 (100%, 87%, and 87%, respectively; see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B757).

Next, we investigated the 177 manually reported events of the total DPS-recorded ingestions (see Figure 2, Supplemental Digital Content, http://links.lww.com/QAI/B757). Because of a known programming error in the app early in the study, 2 participants were instructed to manually log all ingestions until an update was made available. Ingestion data for these 2 participants were downloaded from their Readers at the end of the study period, and all Reader-detected ingestions were reconciled with manually reported ingestions. Overall, accelerometer data from the Readers of all study completers indicated that 89% (n = 158) of manually reported ingestions resulted from a lack of engagement with the Reader or failure to use the Reader according to instructions, and 11% (n = 19) were recorded in instances where reported ingestions were not detected by the Reader despite supporting use metrics (eg, accelerometer data), indicating proper Reader use during ingestions. Given the supporting use metrics, these 19 events were then added to the above number of successful DPS operations (n = 922) for a combined total of 941 instances in which ingestions were successfully detected by the DPS. Therefore, we calculated that ingestion of the digital pill activated the integrated radiofrequency emitter (n = 922) and was detected by the DPS (n = 941) 98% of the time. A Pearson correlation between DPS-recorded ingestions and pill counts demonstrated a strong positive correlation between adherence measured by the DPS and adherence calculated per pill counts (R = 0.91; 95% CI: 0.75 to 0.97; $P < 0.001$).

Correlation of TFV-DP in DBS With DPS Adherence

A total of 29 DBS samples were collected across 15 participants; of which, 22 samples were paired with their corresponding DPS-recorded ingestion reports for the 3 weeks preceding collection and then analyzed. The median concentration of TFV-DP across punches was 971.85 fmol/punch (interquartile range, 873.7), which showed that most participants had TFV concentrations indicative of protection from HIV during the study period. For individuals who had a DBS of ≥700 fmol per punch, indicating ≥4 doses of PrEP ingested per week, the DPS also recorded ≥4 PrEP ingestions. A point–biserial correlation showed a significant moderate to strong positive correlation (R = 0.58; 95% CI: 0.21 to 0.80; $P = 0.047$) between DPS-recorded adherence and TFV-DP in DBS.

Next, we considered both TFV-DP in DBS and DPS-recorded adherence data as continuous variables and calculated Pearson correlation for each TFV-DP concentration at each time point (R = 0.85, 95% CI: 0.57 to 0.95; $P = 0.0002$ at month 1; R = 0.75, 95% CI: 0.17 to 0.94; $P = 0.0197$ at month 3). These correlations demonstrate that DPS-recorded adherence data were closely correlated with adherence quantified using TFV-DP in DBS.

DISCUSSION

Given the unique barriers to PrEP adherence that MSM with substance use face, innovative methods to accurately measure and improve adherence are of critical importance. The need to reach specific weekly thresholds of PrEP adherence suggests that direct, real-time measurements may provide valuable data for those experiencing suboptimal or frank nonadherence to PrEP. This investigation demonstrates that a DPS is feasible, acceptable, an accurate method for measuring PrEP ingestions among HIV-negative MSM who use substances and that it may be suitable for individuals who have difficulty in maintaining adherence.

Despite suboptimal adherence in some individuals, participants were able to successfully resume the use of the DPS and record PrEP ingestion events, even following missed doses. When the DPS was correctly operated, the system was able to accurately record a PrEP ingestion event 98% of the time. Importantly, in individuals who experienced a decrease

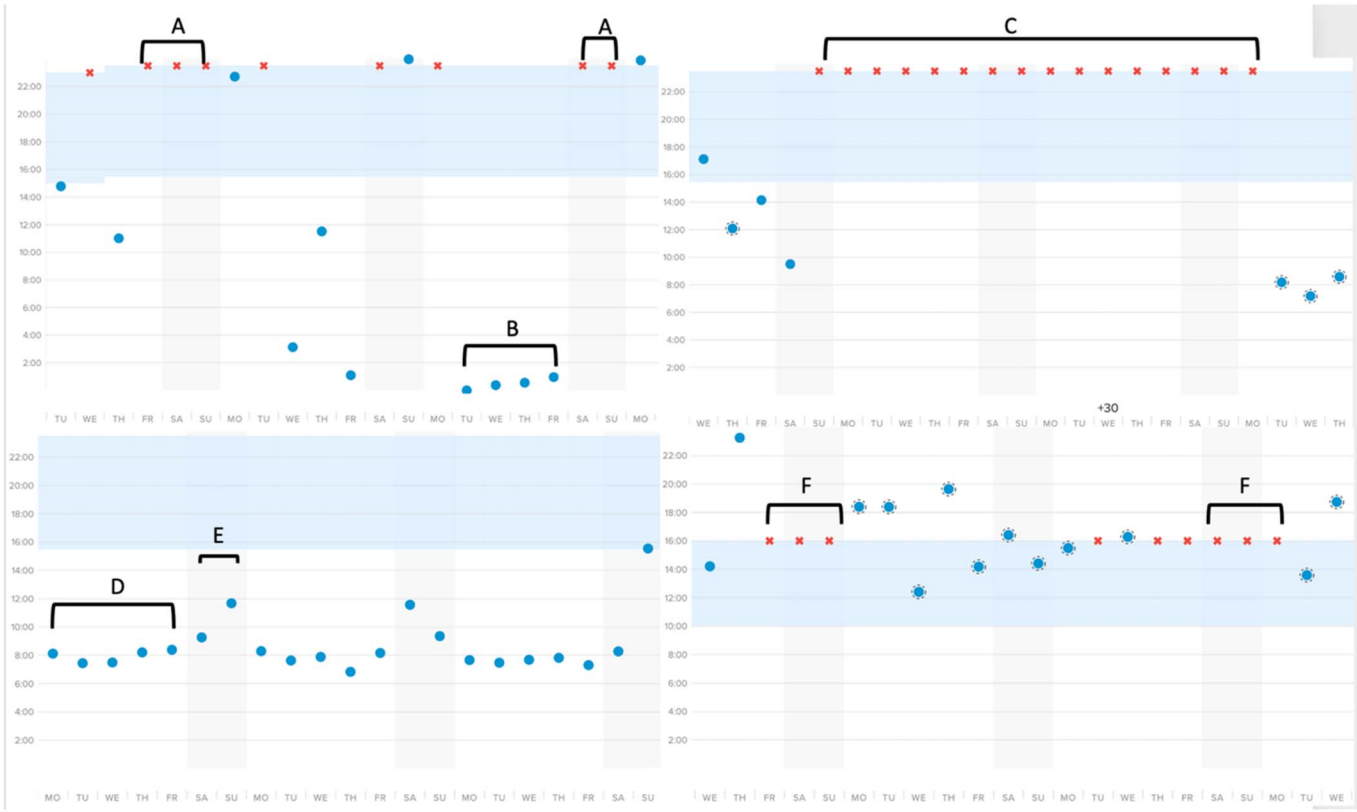

FIGURE 3. DPS-recorded adherence and nonadherence from sample participants. DPS adherence graphs from selected participants illustrating context around patterns of adherence and nonadherence. Identification of weekend substance use leading to nonadherence (A), but a return to PrEP adherence during the week (B); entering a new relationship with a partner who was not accepting of PrEP, resulting in long-term nonadherence (C); temporal changes, from ingesting PrEP with breakfast during the week (D), to liberalized ingestion patterns on weekends (E); and routine changes leading to nonadherence, including visiting a partner's home on weekends (F). Red X = no recorded ingestion during dosing window. Blue circle = DPS-recorded ingestion.

in adherence over the study period, the DPS was able to detect these trends, which strongly correlated with monthly pill counts and data from DBS samples. This suggests that the DPS technology is ready for broader deployment in clinical settings and can potentially signal impending nonadherence before a clinical visit, where PrEP adherence may be discussed with a patient or before DBS data are available. Following a structured training program, participants were able to effectively engage with the DPS and consistently operate it over the 3-month study period.

One key advantage of the DPS is the ability to understand daily adherence patterns. Although other measures of adherence allow for ingestion measurement in aggregate, the DPS can detect suboptimal adherence at the level of individual dosing events, which may occur in the context of other life circumstances relevant to adherence (Fig. 3). Using DPS data, we uncovered several distinct patterns of PrEP ingestion behavior, which were connected to changes in participants' personal lives, disruptions of structured routines, and substance use behavior, all of which resulted in nonadherence. Future interventions could leverage these real-time contextual insights to better understand and address suboptimal adherence before the onset of frank nonadherence. Other aspects of PrEP use, like strategies for achieving preventive-effective adherence, can be monitored and perhaps encouraged through the DPS.[30]

We also found that the number of digital PrEP pills ingested per month could aid in identifying individuals who may benefit most from adherence interventions. Although standard PrEP clinical visits occur every 3 months, we noted that by month 2, some participants demonstrated signs of decreased DPS-recorded ingestions, indicating nonadherence. Such individuals could be potential targets for empirically based interventions to address PrEP nonadherence at the onset. By targeting and addressing real-time barriers to adherence, the DPS can serve not only as a feedback tool to help individuals improve their adherence on a day-to-day basis but also as a method for monitoring the effectiveness of behavioral interventions that are delivered to users at the moment of nonadherence. Over the long term, the DPS may also be deployed as a starter kit for individuals who are PrEP naïve to help teach basic adherence skills over the first few months or as part of a booster package for those who experience persistent lapses in adherence. For these individuals, providing scripted reminders or more complex interventions that present users with personalized DPS adherence data can help to alter the course of their adherence. DPS-recorded adherence patterns may additionally be incorporated

into other sexual health and substance use outcomes to develop machine learning algorithms that detect impending nonadherence, thereby improving the timing, precision, and impact of existing adherence interventions that support both primary and secondary HIV prevention for MSM.[31,32]

In our sample, engagement with the DPS varied from full operation of the technology to ingestions manually reported in the app. For manually reported ingestions, internal device metrics were used to understand whether and how the Reader had been moved at any given time; these metrics helped us to determine whether manually reported ingestions were because of technical errors outside a participant's control or because of nonadherence to the technology. The use of a Reader to capture the radiofrequency signals from ingested digital pills will likely continue to be required until miniaturization of a Reader can allow for the direct transmission of ingestions to a smartphone. Until these capabilities are developed, autonomous detection of how individuals interact with the DPS based on Reader movement may help clinicians understand and differentiate between nonadherence to technology or medication.

We additionally found a correlation between DPS adherence data and TFV-DP in DBS, which is strongly predictive of protection against HIV acquisition.[26,28] Individuals who ingested ≥4 doses of PrEP per week, as indicated by their concentration of TFV-DP in DBS, also had ≥4 DPS-recorded ingestions per week; this correlation remained strong even when TFV-DP in DBS and DPS data were analyzed as a continuous variable, suggesting that participants continue to engage and report objective adherence data through the DPS over time. We also demonstrated a strong correlation with pill counts, which suggests that, with additional research, the DPS can eventually be used as a stand-alone adherence measurement system that is comparable to other techniques for measuring PrEP adherence used in research settings.

Through our qualitative user experience interviews, we found that MSM were accepting DPS, able to successfully troubleshoot, and operate it and willing to engage with it over a 3-month period. This is consistent with our earlier qualitative work indicating multiple driving factors for MSM to accept a DPS.[14] Although we deployed a DPS without additional supporting features, like reminders and interventions to augment day-to-day adherence, participants reported that they would be willing to accept and engage with such messages. For participants, the largest barrier to successful engagement with the DPS continues to be the wearable Reader. We anticipate that ongoing refinements to the technology, including miniaturizing the Reader, may improve the overall acceptability of the DPS. Despite these barriers, participants were willing to operate and engage with the DPS, suggesting that additional research should be conducted to empirically test how this technology—as well as behavioral interventions that can be layered over the DPS—can be leveraged to assess PrEP adherence over the long term. Future work should include the continued development and adaptation of interventions that use DPS data to deliver support proximal to nonadherence events or patterns. Further research should also explore participants' perceptions and preferences for data sharing in the DPS context, as well as the ways in which both personal adherence data and medication regimens can be masked to maximize individual privacy, to inform the development of guidelines to maximize privacy protections for DPS use.

This investigation has several limitations. First, the study was conducted at a single community health center with a focus on lesbian, gay, bisexual, transgender and queer or questioning care and research. Baseline participant PrEP acceptance and willingness to engage with a DPS may vary depending on site and the experiences of providers delivering HIV prevention services. Second, the duration of participants' prior PrEP use may have impacted their use of PrEP and the DPS during the study period; however, data on the duration of participants' PrEP use before enrollment in the study were not collected. Third, the majority of participants were white and well educated. Experiences with and ease of DPS operation are likely to vary based on existing comfort with operating smartphones and technology more generally. Fourth, several opportunities arose during the study for technical improvements related to the DPS, including a malfunctioning app that required a programming correction, as well as a novel protocol that aided in preserving the battery life of the Reader during real-world operation. These changes required participants to use the manual recording feature on the app until new updates were available; this, in turn, may have impacted the overall number of DPS-recorded ingestions. Fifth, the assay used for TFV-DP was different from those previously used to report TFV-DP. These assays have not been cross validated and may result in errors in assayed concentration of TFV-DP. Additionally, we did not record postdose collection timing for DBS results. We anticipate that the contribution of variable timing of postdose DBS collection is minimal given the long half-life of TFV-DP.[26] Finally, although there is no gold standard to measure adherence, we used pill counts as the ground truth against which DPS ingestions were measured. We recognize that participants may have experienced social and research-related pressures to maintain adherence during the study period, and that they may have stockpiled or retained unused pills rather than bringing them to study visits as directed. It is therefore possible that any withholding of pills may have inadvertently decreased the measured accuracy of the DPS, given erroneous pill counts; as such, the real-world accuracy of the DPS in future investigations that do *not* also use pill counts may be higher than that reported in this investigation.

CONCLUSIONS

A DPS is a feasible, acceptable, and accurate method for measuring PrEP adherence patterns in MSM with substance use. Future work surrounding the development of interventions that respond to adherence patterns should incorporate a DPS to generate insights into the contextual basis of suboptimal PrEP adherence that can be used by patients, researchers, and care teams.

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