Real-World Implementation Challenges Associated with a Digital Pill System to Measure Adherence to HIV Pre-Exposure Prophylaxis from Two Studies of Men Who Have Sex With Men

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**Abstract**

*Once-daily oral pre-exposure prophylaxis (PrEP) is highly effective for HIV prevention, but its efficacy is dependent on adherence, which can be challenging for men who have sex with men (MSM) with substance use. Digital pill systems (DPS) represent a novel tool for directly measuring adherence through ingestible radiofrequency sensors that confirm ingestions in real-time. We examined operational challenges across two studies involving DPS to measure PrEP adherence. While most participants successfully operated the system, a number of technological and sociobehavioral challenges requiring intervention were identified across both studies. Technological issues were both system- and participant-related, and were primarily addressed with technical updates and participant re-education, while sociobehavioral issues, including health and housing changes and issues with technology access, warranted innovative solutions. Future research leveraging DPS technology should develop robust supportive infrastructure and mitigation procedures to promptly identify and resolve operational issues to optimize the potential benefits of DPS use.*

**Keywords:** Digital pill systems, ingestible sensors, medication adherence, HIV pre-exposure prophylaxis

# 1. Introduction

Human immunodeficiency virus (HIV) represents an ongoing public health crisis on a global scale. In the United States (US) in 2020, the US Centers for Disease Control and Prevention (CDC) reported 30,635 new infections, with transmissions primarily occurring via sexual activity and/or injection drug use (CDC, 2022). These statistics likely underestimate the true HIV incidence in 2020, however, given the impact of the COVID-19 pandemic on clinic-based testing. Men who have sex with men (MSM) experience health disparities that place them at a disproportionate risk for HIV. In 2019, approximately 69% of new diagnoses in the US were among MSM (CDC, 2021a, 2021b).

Over the last decade, once-daily oral pre-exposure prophylaxis (PrEP) has been empirically demonstrated to be highly efficacious for HIV prevention (Anderson et al., 2012; Doblecki-Lewis et al., 2015), and is recommended by both the US CDC (CDC, 2017) and the World Health Organization (WHO, 2016); however, its effectiveness depends on the degree of adherence. In 2012, the multinational Pre-exposure Prophylaxis Initiative (iPrEX) study demonstrated that once-daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was 99% effective for preventing HIV in MSM with drug levels consistent with daily adherence, and over 90% effective in those who took at least four of seven daily doses per week, but only 76% effective among individuals who took fewer than four doses per week (Anderson et al., 2012; Grant et al., 2010).

Substance use disorders increase the risk of suboptimal PrEP adherence and subsequent HIV infection. In 2018, individuals with substance use accounted for 10% of new infections across the US. In one study of MSM, the use of psychostimulants (e.g., cocaine, methamphetamine, ketamine, and ecstasy) increased the likelihood of same-day PrEP nonadherence by 55%, and next-day nonadherence by 60% (Grov et al., 2019). Substance use in the context of sexual activity is common among MSM (Bourne & Weatherburn, 2017; Brennan-Ing et al., 2014), and use of substances – particularly stimulants – has been associated with increased engagement in condomless anal intercourse, which further increases the risk of HIV infection (Feldman et al., 2015; Hoenigl et al., 2016).

Given the interplay of these risk factors, it is important to develop novel tools to accurately measure PrEP ingestion behavior and address suboptimal adherence in order to reduce HIV transmission in this population. Many techniques for measuring adherence currently exist – in the context of HIV, as well as other disease states – and range from indirect strategies (e.g., self-report, pill counts, pharmacy refill data, and smart pill bottles) to more direct ones (e.g., in-person and video-based directly observed therapy, and pharmacological measures that detect drug levels in blood, urine, or hair) (Bell & Haberer, 2018; Castillo-Mancilla & Haberer, 2018; Spinelli et al., 2020). Though many of these measures represent significant scientific advancements, each strategy is also subject to key disadvantages (e.g., social and desirability biases, and cost and scalability challenges), such that there is still no gold standard for measuring adherence.

## 1.1. Digital pill systems

Digital pill systems (DPS) represent a novel approach for objectively measuring medication adherence in real-time. DPS enable the direct measurement of ingestion events via an ingestible radiofrequency sensor (ID-Tag) that is integrated into a gelatin capsule (ID-Capsule), which overencapsulates a medication (e.g., TDF/FTC; Figure 1) (P. R. Chai, Vaz, Goodman, et al., 2022; Goodman et al., 2022). Upon ingestion of this “digital pill,” the radiofrequency sensor is activated by the chloride ions in gastric fluid, which broadcasts a radiofrequency signal from inside the stomach that is acquired by a wearable Reader device (Figure 1). Ingestion data is stored and then relayed via low energy Bluetooth (BLE) from the Reader to a participant-facing smartphone application (ID-Cap App, Figure 1), as well as to a clinician- or researcher-facing online server, where adherence metrics are displayed on-demand. Participants also have the ability to manually record ingestions in the ID-Cap App, in the event that an ingestion is not recorded by the Reader or confirmation of its detection is not displayed in the ID-Cap App.



**Figure 1. Overview of ID-Cap System components.** The ingestible radiofrequency sensor (ID-Tag) is embedded within a gelatin capsule (ID-Capsule), which over-encapsulates a medication (A). The ID-Tag is activated in the stomach, and the radiofrequency signal is transmitted to the Reader (B). Ingestion data flows from the Reader to the ID-Cap App (C) and online server.Images courtesy of etectRx (Gainesville, FL).

In addition to transmitting ingestion data from the digital pill, the Reader also contains a gyroscope, which allows the device to recognize motion and orientation (e.g., indicating whether the Reader has been moved from the charging pad). Gyroscopic information from the Reader can be used to contextualize both participant-reported technological issues and adherence behavior, and to infer whether the device has been operated correctly (e.g., via motion data consistent with wearing the Reader). Battery life information can also be queried from Readers by etectRx, which can further assist study teams in understanding real-world use behaviors and better troubleshoot technological issues as they arise.

Our prior research has established the overall feasibility of DPS technology for measuring PrEP adherence (P. R. Chai, Mohamed, Bustamante, et al., 2022), as well as acceptability among both prospective and actual users (P. R. Chai et al., 2021; P. R. Chai, Goodman, Bronzi, et al., 2022). We have also established the DPS as a platform technology that permits the delivery of personalized, digital adherence interventions respondent to adherence data (P. R. Chai et al., 2021; P. R. Chai, Mohamed, Bustamante, et al., 2022; P. R. Chai, Mohamed, Goodman, et al., 2022).

According to the Technology Acceptance Model (TAM), real-world adoption of a novel technology is driven by its perceived usefulness and ease of use (Venkatesh & Davis, 2000). This theoretical framework has informed our ongoing implementation work in which we have sought to identify key perceived benefits and barriers to daily operation (P. R. Chai, Mohamed, Bustamante, et al., 2022; P. R. Chai, Mohamed, Goodman, et al., 2022). In response to participant feedback, we developed a standardized, two-part training program – grounded in the TAM – to help new DPS users navigate challenges associated with daily system operation. The program comprises an initial in-person training session, followed by a six-day remote follow-up period with scripted text message check-ins to support DPS operation and basic troubleshooting. An analysis of this pilot program found that participants perceived both the in-person and remote follow-up components to be acceptable (P. Chai et al., 2021).

The aim of this analysis is to describe the operational challenges that occurred in the real-world deployment of a DPS (ID-Cap System, etectRx, Gainesville, FL), across two studies that leveraged DPS technology to measure adherence to once-daily oral TDF/FTC as PrEP in HIV-negative adult MSM with non-alcohol substance use.

# 2. Materials and Methods

## 2.1. Studies included

The DigiPrEP study (NCT03842436) was a single-arm, open-label, pilot demonstration trial (N=15), conducted between March 2019 and April 2020, which evaluated the feasibility, acceptability, and accuracy of a DPS for measuring adherence to PrEP over a 90-day period (P. R. Chai, Mohamed, Bustamante, et al., 2022). Participants completed the standardized training program on DPS operation, which involved both in-person and remote support as described above (P. Chai et al., 2021). We also conducted monthly pill counts and timeline followback discussions to contextualize instances of DPS-detected PrEP nonadherence and evaluate adherence patterns over the study period (P. R. Chai, Mohamed, Bustamante, et al., 2022).

The PrEPSteps study (NCT03512418) is an ongoing pilot randomized controlled trial (current N=23 completers; target N=60) to evaluate the feasibility, acceptability, and potential effectiveness of a cognitive behavioral therapy (CBT)-based, smartphone-delivered adherence intervention that responds to DPS-detected PrEP adherence and nonadherence (P. R. Chai, Mohamed, Goodman, et al., 2022). Participants first complete a 14-day run-in period, in which they utilize the DPS to measure daily PrEP adherence. All participants also complete an initial session of a CBT-based adherence counseling program (LifeSteps) (Safren et al., 1999). They are then randomized to the intervention – i.e., 90 days of DPS use, plus personalized LifeSteps booster messages, containing real-time adherence feedback and support based on PrEP ingestion patterns – or the time-matched control, involving use of the DPS alone without additional adherence support. As in the DigiPrEP study, we evaluate PrEP adherence patterns at monthly study visits and provide technological support in accordance with our standardized DPS training program (P. Chai et al., 2021), as well as ad-hoc support with operational issues as they arise. PrEPSteps participants are followed for an additional three months following completion of the 90-day period of DPS use, in order to assess persistence of PrEP adherence skills.

## 2.2. Recruitment

Participants were recruited for both the DigiPrEP and PrEPSteps studies via existing recruitment databases at the study site, medical record review, provider referrals, and social media and community-based outreach in the greater Boston metropolitan area. Potential participants were pre-screened via phone or in-person by the study team; individuals who met preliminary eligibility criteria were scheduled to attend an in-person study visit to confirm eligibility.

## 2.3. Participants

Participants in both studies met the following inclusion criteria: (1) age 18 or older; (2) cisgender MSM; (3) non-alcohol substance use in the past six months; (4) currently taking or initiating once-daily TDF-FTC as PrEP; (5) qualifying laboratory tests for PrEP (negative rapid HIV test, creatinine, hepatitis B immunization, screening for sexually transmitted infections [STIs]); and (6) owns a smartphone with Android or iOS. PrEPSteps participants were also screened for moderate to severe non-alcohol substance use disorder via the Mini International Neuropsychiatric Interview (MINI) assessment (Sheehan et al., 1998).

Exclusion criteria for both studies were: (1) non-English-speaking; (2) living with HIV; (3) not qualified to take PrEP (e.g., abnormal liver function, or creatinine clearance <60); (4) allergy to gelatin, silver, or zinc (components of digital pill); (5) history of Crohn’s disease or ulcerative colitis; (6) history of bowel surgery, gastric bypass, or bowel stricture; (7) history of gastrointestinal malignancy or radiation to abdomen; and (8) unable or unwilling to ingest digital pills.

## 2.4. Assessment of operational challenges and development of solutions

Throughout both the DigiPrEP and PrEPSteps studies, weekly study team meetings were conducted in collaboration with etectRx, which involved an ongoing review of participants’ adherence data in the online clinician dashboard, as well as discussion of reported technological and sociobehavioral challenges (e.g., participant financial constraints) associated with operation of the DPS. Several mechanisms were used in team discussions to identify operational challenges requiring study team follow-up.

First, in instances where participants contacted members of the study team and specifically requested assistance with the DPS, or reported adherence challenges related to a perceived malfunction of the technology, the study team promptly reviewed these issues with etectRx, and developed appropriate troubleshooting strategies. Such strategies included providing remote technological support to participants via text message and/or phone, and scheduling in-person follow-up visits to resolve outstanding issues.

Second, gyroscopic data from Readers indicating potential patterns of Reader non-use – for example, as detected by a lack of physical contact of the Reader with the charging pad, or a lack of motion of the device – were monitored on an ongoing basis by etectRx. Such information was discussed as a study team when operational issues arose, and was used to contextualize participant-reported operational challenges and better distinguish technological issues that occurred outside of participants’ control (e.g., malfunction of a component of the system) from potential instances of participant disengagement with the DPS. The study team and etectRx reviewed such challenges in detail and jointly troubleshooted solutions (e.g., replacement of malfunctioning component of the system, as applicable), which were implemented by the study team.

Third, sociobehavioral challenges were recorded by the study team during timeline followback discussions conducted at monthly study visits, as well as during ad-hoc correspondence with participants over the course of the study period. These types of challenges were documented and subsequently reviewed among study team members in order to determine an appropriate course of action and resolution (e.g., additional remuneration to enable continued participation, in the event of financial hardship affecting a participant’s ability to utilize the technology).

## 2.5. Analyses

Descriptive statistics were calculated to characterize sample sociodemographics. Operational challenges documented across both studies (i.e., via ad-hoc contact with the study team throughout DPS use, and/or during timeline followback discussions at monthly study visits) were reviewed and collated. Challenges were indexed into overarching categories, and the technological solutions, troubleshooting steps, and management strategies developed and implemented by both the study team and etectRx were summarized.

**3. Results**

## 3.1. Characteristics of samples

A total of 38 enrolled participants across the two studies were included in this analysis. The mean age of the combined sample was 37 years old (SD=9.4). Participants were primarily White (n=26, 68.4%), not Hispanic or Latino (n=31, 81.6%), identified as homosexual or gay (n=32, 84.2%), and held at least a college degree (n=27, 71.1%). Nearly two-thirds of the overall sample owned and operated an iPhone (n=23, 60.5%), versus an Android, during the study period.

**Table 1. Sociodemographic characteristics (N=38)**

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| --- | --- |
|  | **n (%)** |
| **Age** |  |
| Mean (SD) | 37.3 (9.4) |
| **Race** |  |
| American Indian or Alaska Native | 1 (2.6) |
| Asian | 1 (2.6) |
| Black | 3 (7.9) |
| White | 26 (68.4) |
| More than one race | 6 (15.8) |
| Other | 1 (2.6) |
| **Ethnicity** |  |
| Hispanic or Latino | 7 (18.4) |
| Not Hispanic or Latino | 31 (81.6) |
| **Gender** |  |
| Cisgender man | 38 (100) |
| **Sexual orientation** |  |
| Bisexual | 6 (15.8) |
| Homosexual or gay | 32 (84.2) |
| **Education** |  |
| Less than high school | 1 (2.6) |
| High school or GED | 2 (5.3) |
| Some college | 8 (21.1) |
| College degree | 14 (36.8) |
| Some graduate/professional work | 2 (5.3) |
| Graduate/professional degree | 11 (28.9) |
| **Smartphone type** |  |
| Android | 15 (39.5) |
| iPhone | 23 (60.5) |

## 3.2. DPS operational challenges and solutions

Operational issues across both studies were collated and organized into two categories: (1) technological challenges, and (2) sociobehavioral challenges.

**3.2.1. Technological challenges**. Technological issues were organized into two sub-categories: (1) system-related issues with the delivery and display of ingestion data, and functionality of DPS components, and (2) participant-related issues in DPS operation.

System-related challenges primarily included problems with data transmission at three different points – from the ID-Tag (within the ID-Capsule) to the Reader, from the Reader to the ID-Cap App, and from phones to the online server. A variety of technical steps were taken by etectRx to address these issues, including improving ID-Tag manufacturing and screening processes to establish high signal strength, as well as improving the signal detection sensitivity in the Readers, in order to ensure the appropriate capture of ingestion event information. etectRx also identified and corrected several bugs in the Reader software and ID-Cap App – which contributed to data transmission failures from Readers to phones, and from phones to the server – and improved Bluetooth stability and automatic re-pairing capacity to resolve the related transmission issues. In addition, a system communication error caused some issues in the display of ingestion data on the online server, periodically resulting in the appearance of duplicate ingestions. etectRx modified the software to correct the filters in the display of duplicate ingestions and to improve the researcher-facing visualization of ingestion data on the server.

In terms of challenges related to the functionality of DPS component parts, some participants reported charging issues – e.g., malfunctioning charging pads, power bricks (possibly due to an electrical surge), and Readers (possibly due to dropping the device and damaging the charging coil inside the Reader). These were documented by the study team, and, through an internal investigation, etectRx identified a manufacturing issue that had caused several Readers to be produced without the necessary shielding. This issue was corrected, and in parallel, the study team replaced the faulty Readers and charging components for participants to use for the duration of the study period.

Participant-related operational challenges included failing to wear the Reader for sufficient time to allow for detection of a digital pill ingestion, as well as issues pairing the Reader with their phone via Bluetooth prior to ingestions. Other Bluetooth-related issues involved participants switching phones and having difficulty with unpairing the Reader from their old phone and re-pairing it with their new phone. Participants also periodically turned Bluetooth off on their phone (e.g., to save battery, if using an older phone with limited battery power) and forgot to turn it back on prior to a digital pill ingestion. Additional operational challenges included issues with using the wireless charging pad (e.g., failing to place the Reader in the correct position on the charging pad in order to engage the charging coil), correctly placing the Reader on the charging pad but forgetting to plug it into an electrical outlet, and forgetting to charge the Reader at all prior to use.

For each of these issues, the study team reinforced participants’ training and education around the correct operation of the Reader, charging components, and Bluetooth pairing within the ID-Cap App. The study team also developed additional low threshold supports, including providing participants with a physical study card containing the Bluetooth pairing code – which they could easily access in the event that their Reader became disconnected and Bluetooth re-pairing was required – as well as a step-by-step quick start guide with resources to help them autonomously troubleshoot and resolve connectivity and charging issues. etectRx also implemented several updates to the online server and ID-Cap App in response to these operational challenges, including ID-Cap App enhancements to improve Bluetooth pairing and automatic re-pairing, as well as adding diagnostic information on the main screen of the app to alert participants of any issues with the Bluetooth connection between their phone and Reader.

In instances where participants elected to manually record PrEP ingestions in the ID-Cap App, the study team was initially unable to determine in real-time whether these manually reported ingestions were the result of “true” technology failures, or other operational or personal reasons unrelated to the technology itself (e.g., choosing not to use the Reader during an ingestion if short on time). To correct this, etectRx added a feature to the online server, which enabled the study team to review, in real-time, participants’ reported reasons for manually recording their ingestions in the ID-Cap App.

**3.2.2. Sociobehavioral challenges**. A number of sociobehavioral issues also arose across both studies, which were organized into two sub-categories: (1) issues related to changes in participants’ life circumstances, and (2) issues related to participants’ access to technology. Both of these sub-categories represented largely unanticipated barriers to both DPS operation and study engagement.

Some participants faced financial constraints that impacted their ability to operate the DPS during the study period – including, for example, an inability to pay for a phone plan or data plan that would support their ongoing use of the ID-Cap App, or an outstanding Apple bill preventing them from downloading the app at all. In such instances, the study team provided participants with additional remuneration, on a case-by-case basis, in order to alleviate any financial problems that were interfering with their use of the DPS. Limited access to electricity to charge the Reader was an additional challenge that emerged; to address this, the study team began charging participants’ Readers as needed while they were onsite during study visits.

Changes in housing and health status – particularly involving homelessness, hospitalization, and incarceration – also periodically arose as operational challenges. For some participants, substance use during the study period additionally interfered with their ability to operate the DPS. In response to these issues, the study team maintained ongoing contact with participants, as much as possible, to support their retention. The study team documented in detail the impact of such life circumstances on participants’ study engagement, and shared this information with etectRx, in order to contextualize the observed operational challenges in these cases and inform the design of future studies.

Finally, participants’ travel and other changes in daily routines at times posed a challenge to DPS operation. Some participants disengaged from using the DPS to measure their PrEP ingestions while on vacation or otherwise away from home, and reported that they had limited access to the DPS components (including their Reader, charger, or supply of digital pills) during these periods. In response, the study team reinforced training messages with participants around the use of the technology in the context of international travel (i.e., ID-Cap System use is not permissible outside of the US), and documented the impact of such routine-related changes on real-world engagement with the DPS.

**4. Discussion**

The translation of novel technologies into real-world use is often accompanied by operational challenges, particularly in the context of health systems. Empirical exploration of such issues can be highly informative for continued advancement and deployment, and for maximizing “technological affordances” – i.e., the problem-solving capability of a technology (Mora et al., 2021). As many operational challenges may be unanticipated, early-stage pilot trials are particularly important for understanding the clinical value of technologies themselves, as well as the parallel support systems that must be developed for successful implementation in the real world.

While the development of DPS for adherence measurement continues to evolve – with several studies demonstrating its feasibility, acceptability, and potential for an effect on adherence across multiple disease states (Belknap et al., 2013; P. R. Chai et al., 2017; P. R. Chai, Mohamed, Bustamante, et al., 2022; Daar et al., 2020) – less is known about the range of potential operational challenges and specific training and support infrastructure needed to troubleshoot and resolve issues to support DPS use in both research and clinical settings.

Overall, while the majority of participants across the two studies included in this analysis – which used DPS to measure PrEP adherence in MSM with non-alcohol substance use – were able to use the system successfully (P. R. Chai, Mohamed, Bustamante, et al., 2022), this investigation identified a number of operational challenges, suggesting that such issues are likely to occur as DPS technology is leveraged as a tool for adherence measurement and intervention. Moreover, this analysis demonstrated that a robust training and support infrastructure for participants, as well as ongoing coordination between research teams and industry collaborators, are critical to the timely identification and resolution of operational issues.

The majority of technological challenges involved system-related issues with the transmission of PrEP ingestion data (primarily caused by bugs in the ID-Cap App and Reader software), and participant-related operational issues (primarily related to using and charging the Reader, and connecting to the Reader via Bluetooth). Though unanticipated, many of the system-side issues were uncovered based on operational feedback from participants. For example, some reported to the study team that they had ingested a digital pill and worn the Reader per the proper procedure, but noted that the ingestion did not appear on the ID-Cap App; in response to this feedback, etectRx was able to identify the bugs and then rapidly design and implement software modifications and hardware updates to improve the transmission of ingestion data.

While many of the operational challenges on the participants’ side were anticipated, given the novel nature of the system, several were unexpected. Though we projected that participants would have little difficulty operating the wireless charging pad, some found it challenging to correctly place the Reader on the pad to engage the charging coil, as well as to remember to plug the pad into an outlet while in use. These types of unforeseen issues prompted the study team to improve the initial technology training materials and procedures, and to develop enhanced materials for reinforcing proper DPS use throughout the study period.

Most of the sociobehavioral challenges that emerged across both studies, relating to changes in life circumstances and access to technology, were also unanticipated. For example, some faced financial constraints which limited their access to the ID-Cap App (e.g., insufficient phone data plans, or outstanding bills), and some had limited access to electricity to charge the Reader (e.g., due to unstable housing) or relied on public Wi-Fi networks to allow their Reader to upload adherence data to the server. Other life circumstances created temporary disruptions in DPS use, which then led to additional technological challenges – for example, after one participant’s Reader discharged completely during a hospital stay, they subsequently had difficulty with re-pairing to their phone via Bluetooth after recharging and turning the Reader back on.

While some sociobehavioral challenges were voluntarily reported by participants – prompting the development of innovative solutions (e.g., subsidizing phone data plans to enable use of the ID-Cap App, or providing access to electricity to charge Readers) – many were first identified by the study team and etectRx while reviewing adherence data in the online server. Periods of consistent nonadherence were flagged, and internal Reader data (e.g., gyroscopic data indicating a lack of Reader movement and/or loss of battery) was then reviewed to further contextualize DPS-detected nonadherence. Taken together, this information prompted outreach from the study team to check in and assist participants with technological issues as needed. Interestingly, in many cases, issues that were initially interpreted as solely technological eventually exposed key sociobehavioral challenges that were interfering with, and had a compounding effect on, PrEP adherence and DPS use. DPS-detected patterns of nonadherence may be indicative of either true PrEP nonadherence or of issues with operation of the technology (which can then also result in nonadherence); it is therefore critical that future research seek to disentangle these issues.

All of the challenges identified in this investigation highlight the importance of developing a highly adaptable and robust support infrastructure to accompany DPS implementation – both for the purposes of troubleshooting and resolving technological problems, and for managing complex life circumstances – in order to facilitate successful DPS operation in the real world. Such supports should include protocolized strategies to address common, anticipated challenges, such as Reader connectivity, charging, and ID-Cap App operation. Study teams should also implement specific protocols for unexpected challenges, including those that encompass both technological and sociobehavioral issues which may require creative or ongoing solutions. In addition, study teams should aim to distinguish acute issues from longer-term disengagement, utilizing a combination of direct participant feedback, review of DPS-detected adherence data, and review of internal Reader data that may suggest a lack of system use, in order to facilitate prompt, precise intervention.

Additionally, in light of the multiple syndemic conditions known to impact PrEP adherence in this population – including substance use and other mental health comorbidities (Shuper et al., 2020) – future DPS research in the context of HIV prevention should systematically evaluate the effects of syndemic social and behavioral factors on the adoption of and continued engagement with DPS technology, as well as on PrEP adherence as measured by the DPS. Our strategies for identifying, triaging, and mitigating operational and sociobehavioral challenges across both studies – and with a population utilizing a medication regimen that carries stigma (Golub, 2018) – may help to guide future deployments of DPS technology and uncover additional factors that influence PrEP adherence in this group.

This investigation had several limitations. Most participants were well-educated and all owned smartphones; the challenges associated with DPS operation may vary across populations, including those with different levels of education and technological fluency, who may also stand to benefit from DPS-based adherence measurement. Both studies also enrolled from a community health center focused on lesbian, gay, bisexual, transgender and queer or questioning (LGBTQ+) research and clinical care, including PrEP care; baseline willingness to use a DPS for adherence measurement may be different across other health care contexts. In addition, given that technological and sociobehavioral challenges occurred on an ongoing and often interconnected basis, frequency data for each specific operational challenge was not collected and was therefore not available for analysis. Finally, as sample sizes were relatively small, findings may not generalize to all HIV-negative MSM with substance use.

**5. Conclusion**

Though DPS present a unique opportunity to objectively measure adherence behavior, and can be leveraged to deliver real-time supportive adherence interventions, real-world use can involve operational challenges. Across two studies utilizing DPS for PrEP adherence measurement, both system- and participant-related technological and sociobehavioral issues were identified as operational challenges impacting DPS use. While most technological challenges were anticipated as issues that can arise with uptake of any novel technology, some sociobehavioral challenges impacting DPS operation required innovative solutions and intervention. Future research should develop standardized strategies and robust supportive infrastructure to anticipate, identify, and resolve operational issues in order to optimize the potential benefits of DPS technology for adherence measurement.

**6. Disclosures**

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**7. References**

Anderson, P. L., Glidden, D. V., Liu, A., Buchbinder, S., Lama, J. R., Guanira, J. V., McMahan, V., Bushman, L. R., Casapia, M., Montoya-Herrera, O., Veloso, V. G., Mayer, K. H., Chariyalertsak, S., Schechter, M., Bekker, L.-G., Kallas, E. G., & Grant, R. M. (2012). Emtricitabine-tenofovir exposure and pre-exposure prophylaxis efficacy in men who have sex with men. *Science Translational Medicine*, *4*(151), 151ra125-151ra125. https://doi.org/10.1126/scitranslmed.3004006

Belknap, R., Weis, S., Brookens, A., Au-Yeung, K. Y., Moon, G., DiCarlo, L., & Reves, R. (2013). Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. *PLoS ONE*, *8*(1), e53373. https://doi.org/10.1371/journal.pone.0053373

Bell, K. M., & Haberer, J. E. (2018). Actionable adherence monitoring: Technological methods to monitor and support adherence to antiretroviral therapy. *Current HIV/AIDS Reports*, *15*(5), 388–396. https://doi.org/10.1007/s11904-018-0413-0

Bourne, A., & Weatherburn, P. (2017). Substance use among men who have sex with men: Patterns, motivations, impacts and intervention development need. *Sexually Transmitted Infections*, *93*(5), 342–346. https://doi.org/10.1136/sextrans-2016-052674

Brennan-Ing, M., Porter, K. E., Seidel, L., & Karpiak, S. E. (2014). Substance Use and Sexual Risk Differences among Older Bisexual and Gay Men with HIV. *Behavioral Medicine*, *40*(3), 108–115. https://doi.org/10.1080/08964289.2014.889069

Castillo-Mancilla, J. R., & Haberer, J. E. (2018). Adherence measurements in HIV: New advancements in pharmacologic methods and real-time monitoring. *Current HIV/AIDS Reports*, *15*(1), 49–59. https://doi.org/10.1007/s11904-018-0377-0

CDC. (2017). *Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 update: A clinical practice guideline*. Centers for Disease Control and Prevention. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

CDC. (2021a). *Diagnoses of HIV Infection in the United States and Dependent Areas 2019: Special Focus Profiles* (Vol. 32). Centers for Disease Control and Prevention. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-32/content/special-focus-profiles.html

CDC. (2021b). *HIV Surveillance Report, 2019* (Vol. 32). Centers for Disease Control and Prevention. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2018-updated-vol-32.pdf

CDC. (2022). *HIV Surveillance Report, 2020* (Vol. 33). Centers for Disease Control and Prevention. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-33/index.html

Chai, P., Bustamante, M., Goodman, G., Mohamed, Y., Najarro, J., Sullivan, M., Castillo-Mancilla, J., Coyle, R., Mayer, K., Rosen, R., Baumgartner, S., Alpert, P., Boyer, E., & O’Cleirigh, C. (2021). A brief training program to support use of a digital pill system for medication adherence. *JMIR Formative Research*, *5*(4), e26213. https://doi.org/10.2196/26213

Chai, P. R., Carreiro, S., Innes, B. J., Rosen, R. K., O’Cleirigh, C., Mayer, K. H., & Boyer, E. W. (2017). Digital pills to measure opioid ingestion patterns in emergency department patients with acute fracture pain: A pilot study. *Journal of Medical Internet Research*, *19*(1), e19. https://doi.org/10.2196/jmir.7050

Chai, P. R., Goodman, G., Bustamante, M., Mendez, L., Mohamed, Y., Mayer, K. H., Boyer, E. W., Rosen, R. K., & O’Cleirigh, C. (2021). Design and delivery of real-time adherence data to men who have sex with men using antiretroviral pre-exposure prophylaxis via an ingestible electronic sensor. *AIDS and Behavior*, *25*(6), 1661–1674. https://doi.org/10.1007/s10461-020-03082-y

Chai, P. R., Goodman, G. R., Bronzi, O., Gonzales, G., Baez, A., Bustamante, M. J., Najarro, J., Mohamed, Y., Sullivan, M. C., Mayer, K. H., Boyer, E. W., O’Cleirigh, C., & Rosen, R. K. (2022). Real-World User Experiences with a Digital Pill System to Measure PrEP Adherence: Perspectives from MSM with Substance Use. *AIDS and Behavior*, *26*(7), 2459–2468. https://doi.org/10.1007/s10461-022-03594-9

Chai, P. R., Mohamed, Y., Bustamante, M. J., Goodman, G. R., Najarro, J., Castillo-Mancilla, J., Baez, A., Bronzi, O., Sullivan, M. C., Pereira, L. M., Baumgartner, S. L., Carnes, T. C., Mayer, K. H., Rosen, R. K., Boyer, E. W., & O’Cleirigh, C. (2022). 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. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *89*(2), e5–e15. https://doi.org/10.1097/QAI.0000000000002854

Chai, P. R., Mohamed, Y., Goodman, G., Bustamante, M. J., Sullivan, M. C., Najarro, J., Mendez, L., Mayer, K. H., Boyer, E. W., O’Cleirigh, C., & Rosen, R. K. (2022). Development of a digital pill and respondent behavioral intervention (PrEPSteps) for HIV pre-exposure prophylaxis adherence among stimulant using men who have sex with men. *Translational Behavioral Medicine*, *12*(1), ibab117. https://doi.org/10.1093/tbm/ibab117

Chai, P. R., Vaz, C., Goodman, G. R., Albrechta, H., Huang, H., Rosen, R. K., Boyer, E. W., Mayer, K. H., & O’Cleirigh, C. (2022). Ingestible electronic sensors to measure instantaneous medication adherence: A narrative review. *Digital Health*, *8*, 205520762210831. https://doi.org/10.1177/20552076221083119

Daar, E. S., Rosen, M. I., Wang, Y., Siqueiros, L., Shen, J., Guerrero, M., Xiong, D., Dao, J., Young, T., Corado, K., Fletcher, C. V., & Liu, H. (2020). Real‐time and wireless assessment of adherence to antiretroviral therapy with co‐encapsulated ingestion sensor in HIV-infected patients: A pilot study. *Clinical and Translational Science*, *13*(1), 189–194. https://doi.org/10.1111/cts.12701

Doblecki-Lewis, S., Cohen, S., & Liu, A. (2015). Clinical treatment options infectious diseases: Update on PrEP implementation, adherence, and advances in delivery. *Current Treatment Options in Infectious Diseases*, *7*(2), 101–112. https://doi.org/10.1007/s40506-015-0046-4

Feldman, M. B., Thomas, J. A., Alexy, E. R., & Irvine, M. K. (2015). Crystal methamphetamine use and HIV medical outcomes among HIV-infected men who have sex with men accessing support services in New York. *Drug and Alcohol Dependence*, *147*, 266–271. https://doi.org/10.1016/j.drugalcdep.2014.09.780

Golub, S. A. (2018). PrEP Stigma: Implicit and Explicit Drivers of Disparity. *Current HIV/AIDS Reports*, *15*(2), 190–197. https://doi.org/10.1007/s11904-018-0385-0

Goodman, G. R., Vaz, C., Albrechta, H., Boyer, E. W., Mayer, K. H., O’Cleirigh, C., & Chai, P. R. (2022). Ingestible Electronic Sensors for Monitoring Real-time Adherence to HIV Pre-exposure Prophylaxis and Antiretroviral Therapy. *Current HIV/AIDS Reports*, *19*(5), 433–445. https://doi.org/10.1007/s11904-022-00625-x

Grant, R. M., Lama, J. R., Anderson, P. L., McMahan, V., Liu, A. Y., Vargas, L., Goicochea, P., Casapía, M., Guanira-Carranza, J. V., Ramirez-Cardich, M. E., Montoya-Herrera, O., Fernández, T., Veloso, V. G., Buchbinder, S. P., Chariyalertsak, S., Schechter, M., Bekker, L.-G., Mayer, K. H., Kallás, E. G., … Glidden, D. V. (2010). Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine*, *363*(27), 2587–2599. https://doi.org/10.1056/NEJMoa1011205

Grov, C., Rendina, H. J., John, S. A., & Parsons, J. T. (2019). Determining the roles that club drugs, marijuana, and heavy drinking play in PrEP medication adherence among gay and bisexual men: Implications for treatment and research. *AIDS and Behavior*, *23*(5), 1277–1286. https://doi.org/10.1007/s10461-018-2309-9

Hoenigl, M., Chaillon, A., Moore, D. J., Morris, S. R., Smith, D. M., & Little, S. J. (2016). Clear links between starting methamphetamine and increasing sexual risk behavior: A cohort study among men who have sex with men. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *71*(5), 551–557. https://doi.org/10.1097/QAI.0000000000000888

Mora, L., Kummitha, R. K. R., & Esposito, G. (2021). Not everything is as it seems: Digital technology affordance, pandemic control, and the mediating role of sociomaterial arrangements. *Government Information Quarterly*, *38*(4), 101599. https://doi.org/10.1016/j.giq.2021.101599

Safren, S. A., Otto, M. W., & Worth, J. L. (1999). Life-steps: Applying cognitive behavioral therapy to HIV medication adherence. *Cognitive and Behavioral Practice*, *6*(4), 332–341. https://doi.org/10.1016/S1077-7229(99)80052-2

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Shuper, P. A., Joharchi, N., Bogoch, I. I., Loutfy, M., Crouzat, F., El-Helou, P., Knox, D. C., Woodward, K., & Rehm, J. (2020). Alcohol consumption, substance use, and depression in relation to HIV Pre-Exposure Prophylaxis (PrEP) nonadherence among gay, bisexual, and other men-who-have-sex-with-men. *BMC Public Health*, *20*(1), 1782. https://doi.org/10.1186/s12889-020-09883-z

Spinelli, M., Haberer, J., Chai, P., Castillo-Mancilla, J., Anderson, P., & Gandhi, M. (2020). Approaches to objectively measure antiretroviral medication adherence and drive adherence Interventions. *Current HIV/AIDS Reports*, *17*(4), 301–314. https://doi.org/10.1007/s11904-020-00502-5

Venkatesh, V., & Davis, F. D. (2000). A theoretical extension of the Technology Acceptance Model: Four longitudinal field studies. *Management Science*, *46*(2), 186–204. https://doi.org/10.1287/mnsc.46.2.186.11926

WHO. (2016). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach, 2nd edn.* World Health Organization. https://www.who.int/publications/i/item/9789241549684

**Appendix**

**Table 2. Examples of real-world DPS operational challenges, solutions, and strategies used**

|  |  |  |
| --- | --- | --- |
| **Type of Challenge** | **Example(s) of Challenge** | **Solutions and Strategies for Management** |
| **TECHNOLOGICAL** |
| **Data Delivery and Display & Functionality of DPS Components** |
| Transmission of ingestion data from ID-Tag to Reader  | Ingestion data from ID-Tag periodically not received by Reader | * etectRx improved signal strength of ID-Tags
* etectRx improved signal detection sensitivity in Reader
* etectRx improved study team ability to identify usage errors in real-time
 |
| Transmission of data from Reader to phone | Ingestion data from Reader periodically not relayed to ID-Cap App | * etectRx added debug code to ID-Cap App to more quickly identify failure issues
* etectRx improved Bluetooth connection stability and automatic re-pairing
* etectRx corrected error in Reader software causing transmission of partial data sets
 |
| Transmission of data from phone to server | Ingestion data received by ID-Cap App periodically not relayed to server | * etectRx identified and corrected logic causing data relay failure in ID-Cap App
* etectRx improved ability to transmit large data sets from Reader after period of disconnection
 |
| Visualization of data on server | Duplicate ingestions displayed on server due to communication errors  | * etectRx modified software to correctly filter display of duplicate ingestions
 |
| Charging components  | Malfunctioning charging pad, power brick, or charging coil inside Reader | * Study team replaced charging components for participant use during duration of study
* etectRx identified and corrected manufacturing issue with Reader shielding
 |
| **Participant Operation of DPS** |
| Reader | Failure to wear Reader for sufficient time during ingestion; failure to turn on and pair Reader before ingestion; failure to launch ID-Cap App before ingestion | * Study team improved and reinforced training procedures for Reader operation
* etectRx enabled ID-Cap App to run in background on phone, eliminating need to launch app before ingestion
 |
| Bluetooth | Difficulty pairing Bluetooth to phone; paired Bluetooth outside of ID-Cap App; switched phones during study period and did not re-pair Bluetooth correctly; turned Bluetooth off to save battery | * Study team improved and reinforced training procedures for Bluetooth pairing
* etectRx updated ID-Cap App to improve pairing utility and enhance automatic re-pair
* etectRx added diagnostic alerts on ID-Cap App for Bluetooth status issues
 |
| Charging procedures | Failure to charge Reader; lack of use of charging pad or USB charging cord; use of outlet not connected to electricity | * Study team improved and reinforced training procedures for charging Reader
 |
| Manually recorded ingestions | Study team unable to determine if manually recorded ingestions due to technology failures or other reasons | * etectRx added server feature to enable real-time review of reasons for manually recorded ingestion in ID-Cap App
 |
| **SOCIOBEHAVIORAL** |
| **Participant Life Circumstances** |
| Financial constraints | Inability to pay for phone or data plan to use ID-Cap App; lack of access to electricity to charge Reader | * Study team provided additional remuneration to alleviate financial issues
* Study team charged Readers during participants’ study visits as needed
 |
| Change in housing or health status | Homelessness; hospitalization; incarceration | * Study team maintained periodic contact and documented impact on study engagement
 |
| Substance use | Substance use-related impairment in ability to operate DPS | * Study team maintained periodic contact and documented impact on study engagement
 |
| Travel or other change in routine | Issues with access to DPS components or medication due to travel or other change in daily routine | * Study team reinforced training guidance around use of DPS during travel and documented impact on study engagement
 |
| **Participant Access to Technology** |
| Phone access  | Limited access to phone due to misplacing or breaking device | * Study team assisted with re-downloading ID-Cap App and re-pairing with Reader
 |
| Reader access | Limited access to Reader due to misplacing device | * Study team replaced Reader for participant use during duration of study
 |
| ID-Cap App access | Limited access to ID-Cap App due to insufficient data, phone storage, or outstanding Apple bills  | * Study team provided additional remuneration to alleviate financial issues
 |
| Internet access | Limited access to Wi-Fi or internet at home or in community | * Study team instructed participants to connect to Wi-Fi while onsite at study visits
 |