



# BMJ Open Attitudes towards participating in research involving digital pill systems to measure oral HIV pre-exposure chemoprophylaxis: a cross-sectional study among men who have sex with men with substance use in the USA

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## ABSTRACT

**Objectives** This quantitative survey sought to understand, among men who have sex with men (MSM) with potentially problematic substance use, the attitudes towards participation in research involving digital pill systems (DPS) for HIV pre-exposure prophylaxis (PrEP) adherence measurement, and the barriers and facilitators to research participation.

**Design** One-time, cross-sectional, online sampling-based survey.

**Setting** US social networking app predominantly focused on MSM.

**Participants** MSM without HIV who reported current use of oral PrEP, potentially problematic substance use and sexual activity in the past 3 months. A total of 157 participants were eligible, passed validity checks and enrolled.

**Outcome measures** Perceptions of DPS usefulness, accuracy and usability (System Usability Scale (SUS)); willingness and motivations to participate in DPS research; preferences for access to and feedback on DPS adherence data; data sharing considerations; and medical mistrust (Group-Based Medical Mistrust Scale (GBMMS)).

**Results** Most of the sample (N=157) was white (n=119, 75.8%), gay (n=124, 79.0%) and cisgender (n=150, 95.5%). The median age was 33 years (IQR: 14). The mean GBMMS score was 13.5 (SD=5.2), and the median SUS score was 70 (IQR: 27.5). In the past 3 months, 36.3% (n=57) reported frequent use of substances before or during sex, and 62.4% (n=98) engaged in condomless sex. While most were adherent to PrEP, approximately 34.4% (n=54) expressed significant worry about daily adherence. Participants wished to monitor their PrEP adherence daily (n=66, 42.0%) and 52% (n=82) were very willing to participate in DPS-based research. The majority were minimally concerned about sharing DPS-detected adherence data with research teams (n=126, 80.3%), and were extremely willing to share these data with healthcare providers (n=109, 69.4%).

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This investigation contributes larger-scale quantitative data on the feasibility of developing the digital pill system among a national sample of men who have sex with men who are behaviourally vulnerable to HIV.
- ⇒ This investigation uses validated instruments to assess system usability, substance use and medical mistrust.
- ⇒ The sample was evenly distributed across US census regions.
- ⇒ This study is based on self-report data, which is vulnerable to bias.
- ⇒ The sample was composed of mostly white, non-Hispanic/Latinx individuals who were engaged in sexual healthcare, who own a smartphone and participate in online dating.

**Conclusions** In this sample, MSM without HIV who use substances reported willingness to use DPS to measure PrEP adherence in a research context, and identified benefits to accessing real-time, DPS-detected adherence data.

## INTRODUCTION

Substance use, condomless sex and psychosocial comorbidities are associated with increased risk of HIV acquisition. Over the past decade, multiple pharmacotherapies have been developed for oral and injectable HIV pre-exposure prophylaxis (PrEP).<sup>1</sup> In 2012, pivotal clinical trials demonstrated that tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was greater than 90% efficacious in preventing HIV among individuals with drug levels consistent with taking four or more doses of TDF/FTC per week, and over



99% effective for those adherent to daily use.<sup>2</sup> As a result, PrEP is now recommended by the US Centers for Disease Control and Prevention and the WHO to prevent HIV acquisition.<sup>3–7</sup> Despite the efficacy of PrEP, adherence challenges exist, especially among men who have sex with men (MSM) who use substances. Substance use disorder and its concomitant syndemic conditions—including trauma, stigma and disengagement from medical care—lead to difficulties in PrEP initiation and persistence.<sup>8–10</sup> Injectable formulations of PrEP, notably long-acting cabotegravir, have recently been found in randomised controlled trials to be efficacious for preventing HIV acquisition.<sup>11</sup> Despite this, there have been concerns regarding new models of adherence with long-acting PrEP, and the spectre for potential integrase-inhibitor resistance in the setting of missed acute HIV infection with starting long-acting PrEP or resistance surrounding early stoppage of injectable PrEP.<sup>12,13</sup> Additionally, certain patient populations may not accept a long-acting injectable PrEP formulation, or may experience adverse events at the injection site that may limit their use.<sup>14</sup> For these reasons, the continued enhancement of oral PrEP adherence remains of critical importance globally. There is, therefore, a continued need to measure mediators of PrEP adherence among individuals with substance use in order to develop adherence interventions to support PrEP use in this population.

Multiple measures of adherence have been developed to advance the management of PrEP.<sup>15</sup> These include indirect measures, such as self-report and pharmacy refill data, as well as direct measures, such as video-facilitated directly observed therapy and biological measures in dried blood spots, urine or hair.<sup>16</sup> Data from adherence measurement tools, such as electronic pill bottles, have been used in prior work to deliver near real-time medication reminders in an effort to boost PrEP adherence.<sup>17</sup> Additionally, adherence measures including self-report and biological measures may inform periodic risk assessments tailored to individual PrEP ingestion patterns.<sup>18</sup> One novel tool for directly measuring adherence, digital pill systems (DPS), detect ingestion events in real time.<sup>16,19</sup> The DPS comprises an ingestible radiofrequency emitter integrated into a standard gelatin capsule, which over-encapsulates the desired medication (eg, PrEP). Once ingested, the digital pill is activated by chloride ions in the stomach, emitting a specific radiofrequency signal that is acquired by a wearable Reader device. The Reader collects ingestion data and transmits it to a cloud-based server, which displays real-time adherence data to patients and clinicians. This technological advancement may facilitate the development of context-aware interventions to teach adherence skills that are respondent and tailored to individual ingestion patterns.

Prior work has demonstrated that DPS are feasible and accurate for measuring medication ingestion events among MSM on PrEP who use substances,<sup>20</sup> and qualitative studies have found that MSM perceive the DPS as useful for improving accountability surrounding PrEP

adherence.<sup>21</sup> DPS technology has also been used to study ingestion patterns in the context of antidiabetic agents, antihypertensive agents, HIV antiretroviral therapy (ART) and antituberculosis therapy.<sup>22,23</sup> These investigations have demonstrated that DPS users perceive real-time feedback via smartphone reminders or app notifications to be valuable for reinforcing their adherence behaviour. Moreover, in one study among persons living with HIV, adherence to oral ART as measured by a DPS was correlated with improvements in HIV viral load detection.<sup>22</sup>

In this investigation, we conducted a quantitative assessment of MSM without HIV who self-reported oral PrEP use, potentially problematic substance use, and recent sexual activity, in order to understand the perceived usability of DPS, and factors that impact willingness to participate in DPS-based HIV prevention research studies.

## METHODS

### Study design and participants

We did a one-time, cross-sectional, online sampling-based survey in the context of a US social networking app predominantly focused on MSM. Participants met the following inclusion criteria: (1) 18 years or older; (2) cisgender or transgender MSM; (3) self-reported HIV-negative serostatus; (4) currently taking oral PrEP; (5) self-reported sexual activity in the past 3 months; (6) score of  $\geq 2$  on the CAGE Questions Adapted to Include Drug Use (CAGE-AID),<sup>24</sup> indicating potentially problematic substance use<sup>25</sup> and (7) current Grindr user.

### Recruitment

Participants were recruited via an ad partnership with Grindr (West Hollywood, California, USA), a social networking app for gay, bisexual, transgender and non-binary individuals, which reported over 13 million users in 2020.<sup>26</sup> In January 2022, an inbox message was delivered to 1 000 000 US Grindr users for 24 hours. Individuals who opened the message were prompted to click a study advertisement, which included a link to a brief eligibility screener. An electronic validity check (CAPTCHA question) was administered after the screener to verify that respondents were human and not automatic computer programs (ie, 'bots').

Eligible individuals who completed the electronic validity check were presented with a fact sheet containing information about the study and survey contents. They were prompted to click 'I agree to participate', which served as documentation of consent.

### Quantitative survey

Using a computer-assisted self-interviewing secure platform, participants completed a cross-sectional quantitative assessment, which included a video overviewing DPS components and functionality, and a series of questions about the DPS. The survey took approximately 30–60 min. To maintain the confidentiality of the sample,

no identifying information was obtained from participants via the survey.

The following manual validity checks were then conducted to verify eligibility for remuneration: (1) age matched date of birth; (2) valid US zip code; (3) home zip code matched home state and (4) IP address confirmed location within the USA.

### Measures

The measures assessed via the quantitative survey are detailed below.

#### Sociodemographics

Age, race, ethnicity, gender, sexual orientation, education, annual income, relationship status and geographical region of the USA were collected via self-report.

#### PrEP use

On a series of discrete items, participants self-reported duration of use, adherence, primary reason for use and level of worry about daily PrEP adherence.

#### Sexual history

Participants reported their number of sexual partners during the past 3 months, as well as STI diagnoses, condom use and substance use before or during sex during the past 3 months. The timing of and reasons for seeking their most recent HIV test, as well as the duration of Grindr use, were also collected.

#### Substance use

Substance use was assessed via the WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) measure.<sup>27</sup> The ASSIST contains eight questions, covering alcohol, tobacco, marijuana, cocaine, amphetamine, inhalants, sedatives, hallucinogens, opioids and other substances. Risk scores for each substance are calculated and categorised into 'low' (0–10 for alcohol, 0–3 for all other substances), 'moderate' (11–26 for alcohol, 4–26 for all others) and 'high' risk (27+for all substances, including alcohol).<sup>27</sup>

#### Medical mistrust

Participants completed an adapted, six-item version of the Group-Based Medical Mistrust Scale (GBMMS) to evaluate mistrust in research and medical settings.<sup>28</sup> The GBMMS is composed of six questions that are scored using a 5-point Likert-scale (1=strongly disagree, 5=strongly agree). Total scores on the adapted GBMMS range from 6 to 25, with higher mean scores indicating greater mistrust.<sup>28</sup>

#### Prior research experience

Participants also reported prior participation in PrEP-related and/or substance use-related research studies.

#### Perceptions of DPS technology

The majority of the survey focused on DPS technology, feasibility and ethical implications for research (online supplemental material 1). Participants reviewed photos

and diagrams of DPS components, and then watched a brief video (recorded by PC) overviewing the basic functionality of DPS (online supplemental material 1). Survey questions covered overall perceptions of the technology; willingness to participate in future DPS-based studies (and reasons for willingness to participate); preferences for access to, and feedback on, DPS adherence data; and data sharing considerations in the research context. Responses to all questions using 5-point Likert scales (1=not at all, 2=slightly, 3=moderately, 4=very, 5=extremely) were collapsed into 3-point scales ('minimal'=1 and 2, 'moderately'=3, 'extremely'=4 and 5). Participants also completed the 10-item System Usability Scale (SUS)<sup>29</sup> to assess the perceived usability of DPS technology; mean SUS scores were calculated. SUS scores greater than 68 are considered above average—indicating a highly usable system. The survey was developed by the investigators (PC, GRG, HA and CF), and piloted among team members to ensure comprehension.

#### Data analysis

All analyses were completed by using SAS version 9.4.<sup>30</sup> To characterise the sample and to address the first aim of the study—understanding potential usability of the DPS—the primary analysis included examining univariate statistics (frequency distributions, measures of central tendency) on all variables. To address the second aim of the study—examining factors that impact willingness to participate in DPS-based HIV prevention research—a series of bivariate tests were conducted leading to a multivariable, multinomial logistic regression model. Given this is an exploratory study in a novel area, bivariate association tests (Fisher's exact; Wilcoxon ranked sum) were completed to determine which predictors should be included in final multivariable model. Bivariate tests were examined between willingness to participate in DPS research (the three-level ordinal outcome variable) and select study variables hypothesised to potentially influence the study outcome (eg, annual income, medical mistrust perceived DPS usability and worry about daily PrEP adherence). Variables with a significant bivariate association at  $\alpha=0.05$  with the study outcome were included in the final multivariable model.

Based on this, the final set of predictors included annual income, medical mistrust (GBMMS score), and perception of DPS usability (SUS score). While daily PrEP worry was not statistically significant at  $\alpha=0.05$ , it was also included in the multivariable model, given its clinical significance with the study outcome. Further, given that MSM who use substances are at increased risk for PrEP adherence issues,<sup>8–10</sup> substance use in the context of sexual activity was included as a predictor. We treated the final outcome (willingness to participate in DPS-based research) as an ordinal scaled variable. Thus, the final multivariable, multinomial logistic regression examined if the above listed predictors were associated with the outcome—willingness to participate in DPS-based research.

## Patient and public involvement

None.

## RESULTS

### Eligibility and survey completion

Of the 1 000 000 Grindr users who received the inbox message containing the study advertisement, 66 400 opened the message (6.6%). Of these, 3475 clicked on the advertisement (5.2%) and were directed to the screener. Of 983 individuals who completed the screener (28.3%), 715 were ineligible (72.7%) due to not currently using oral PrEP (51.3%) and/or not scoring  $\geq 2$  on the CAGE-AID substance use questions (78.6%). Of 268 eligible individuals (27.3%), 239 consented (89.2%) and 175 completed the survey via Qualtrics (73.2%). Eighteen individuals did not pass all validity checks and were removed from the sample, resulting in a final dataset of 157 participants (online supplemental eFigure 1).

### Characteristics of the sample

The median age was 33 years (N=157, range: 18–70, IQR: 14), and most identified as white (n=119, 75.8%), cisgender (n=150, 95.5%), homosexual or gay (n=124, 79.0%) and non-Hispanic/Latinx (n=123, 78.4%). Most had completed at least some college (n=144, 91.7%) and reported an annual income of less than US\$60 000 (n=90, 57.3%). Participants were evenly distributed across US census regions (n=44, 28.0% Northeast; n=28, 17.8% Midwest; n=47, 29.9% South and n=38, 24.2% West) (table 1).

Most participants (n=149, 94.9%) reported taking  $\geq 4$  of 7 PrEP doses per week during the past 3 months, and 59% (n=93) reported being on PrEP for over a year. Despite high self-reported adherence rates, most endorsed at least moderate worry about daily PrEP adherence (n=93, 59.2%). Participants reported a median of six sexual partners in the past 3 months (range: 1–75, IQR: 7); most had been tested for HIV within the past 3 months (n=136, 86.6%) and over a quarter had a diagnosed STI during that timeframe (n=44, 28.0%). Additionally, 62.4% (n=98) reported condomless sex, and 36.3% (n=57) reported substance use before or during sexual encounters in the past 3 months. Half the sample reported using Grindr for more than 5 years (n=80, 51.0%). Substance-related risk was common, with many participants categorised as moderate risk (n=62, 39.5% for alcohol; n=81, 51.6% for marijuana; n=67, 42.7% for tobacco; n=43, 27.4% for inhalants and n=36, 22.9% for amphetamine; details in online supplemental eTable 1). The majority had never participated in PrEP or substance use research (n=147, 93.6%), and the mean GBMMS score was 13.5 (SD=5.2), suggesting a high degree of trust in medical and research spheres (online supplemental eTable 2 and table 1).

### Overall perceptions of DPS usefulness, accuracy and usability

Many participants reported that the DPS would be extremely useful for helping them maintain adherence to

**Table 1** Sociodemographics and select characteristics of the sample (N=157)

Sociodemographics	N (%)
Age	
Median (IQR)	33 (14)
Range	18–70
Race*	
White	119 (75.8)
Black	7 (4.5)
Asian	6 (3.8)
American Indian or Alaska Native	2 (1.3)
More than one race	19 (12.1)
Other	4 (2.5)
Ethnicity	
Not Hispanic or Latinx	123 (78.3)
Hispanic or Latinx	34 (21.7)
Gender Identity	
Cisgender male	150 (95.5)
Transgender male (female to male)	7 (4.5)
Sexual orientation	
Homosexual or gay	124 (79.0)
Bisexual	29 (18.5)
Other	4 (2.5)
Education	
High school graduate/GED or less	13 (8.3)
Some college or college graduate	93 (59.2)
Some graduate school or graduate degree	51 (32.5)
Annual income	
Less than US\$18 000	38 (24.2)
US\$18 000–US\$23 999	11 (7.0)
US\$24 000–US\$29 999	13 (8.3)
US\$30 000–US\$59 999	28 (17.8)
US\$60 000 or more	67 (42.7)
Relationship status	
Single	100 (63.7)
Committed relationship or domestic partnership	32 (20.4)
Open relationship	1 (0.6)
Married	15 (9.6)
Divorced or separated	9 (5.7)
Geographic location (in USA)	
Northeast	44 (28.0)
Midwest	28 (17.8)
South	47 (29.9)
West	38 (24.2)
PrEP use	N (%)
Duration of PrEP use	
Less than 1 month	7 (4.5)

Continued

**Table 1** Continued

Sociodemographics	N (%)
1–6 months	35 (22.3)
7–12 months	22 (14.0)
More than 1 year	93 (59.2)
Self-reported PrEP adherence in past 3 months	
Less than 4 of 7 doses per week	8 (5.1)
4 or more of 7 doses per week	149 (94.9)
Primary reason for PrEP use	
Prevent potential HIV infection	152 (96.8)
Recommended by a physician	2 (1.3)
Recommended by a friend	2 (1.3)
Other	1 (0.6)
Worry about daily PrEP adherence	
Minimally	64 (40.8)
Moderately	39 (24.8)
Extremely	54 (34.4)
Sexual history	
N (%)	
No of sexual partners in past 3 months	
Median (IQR)	6 (7)
Range	1–75
STI diagnosis in past 3 months	
Yes	44 (28.0)
No	113 (72.0)
Condom use during sex in past 3 months	
Never or almost never	98 (62.4)
Sometimes	35 (22.3)
Almost every time or every time	24 (15.3)
Substance use before or during sex in past 3 months	
Never or almost never	44 (28.0)
Sometimes	56 (35.7)
Almost every time or every time	57 (36.3)
Medical mistrust	
N (%)	
Group-Based Medical Mistrust Scale Score	
Mean (SD)	13.5 (5.2)
Prior research experience	
N (%)	
Prior participation in PrEP/substance use research	
Yes	8 (5.1)
No	147 (93.6)
Unknown	2 (1.3)

\*Participants were able to select more than one race  
GED, graduate education development test; PrEP, pre-exposure prophylaxis.

PrEP (n=64, 40.8%), increasing their personal accountability for PrEP adherence (n=91, 58.0%) and enabling a research team to monitor their adherence (n=137, 87.3%) (table 2). The DPS was also perceived to be extremely useful as an adherence support tool for those

initiating PrEP for the first time (n=84, 53.5%). More than half the sample was extremely trusting that the DPS-detected adherence data would be accurate (n=88, 56.1%). Overall, the median SUS score was 70 (IQR: 27.5), indicating above-average perceived usability of the DPS (table 2).

### Willingness and motivations to participate in DPS research

The majority of participants reported being extremely (n=82, 52.2%) or moderately (n=32, 20.4%) willing to participate in future, hypothetical research involving the use of DPS for adherence measurement (table 3). Willingness to participate was driven by a number of motivations, which primarily included monetary compensation (n=108, 68.8% rated this extremely important), contributing to PrEP adherence research (n=105, 66.9% extremely important), and having a novel method through which to access PrEP adherence data (n=92, 58.6% extremely important). Access to PrEP at no cost was also viewed as a motivating factor (n=91, 58.0% extremely important), in addition to participation as an opportunity to discuss PrEP adherence with a study team (n=63, 40.1% extremely important) (table 3).

With respect to differences in willingness to participate in DPS-based research across the sample, participants who reported using substances during or before sex (every time in the past 3 months) were 2.9 times more willing to participate, compared with those with less frequent substance use before or during sex, after adjusting for income, daily worry about PrEP adherence, GBMMS score and SUS scores (aOR 2.9; 95% CI 1.3 to 6.7; p=0.01) (online supplemental eTable 2).

### Preferences for access to and feedback on DPS adherence data

Most participants reported a willingness to be contacted if non-adherent to PrEP via text message (n=125, 79.6%) or notification within the DPS app (n=101, 64.3%). Less than half wanted daily or on-demand access to their adherence data (n=66, 42.0%), yet perceived this option to be a key component of DPS technology more generally (table 2). Participants reported that an in-app calendar function would be an extremely useful method to access adherence information (n=96, 61.1%) (table 4). More than half reported that weekly text messages containing an adherence score (ie, number of ingested pills detected during the prior 7 days) would be extremely useful (n=93, 59.2%). Nearly half perceived weekly text messages from the system containing a similar adherence summary, but reported in percentage format, to be extremely useful (n=76, 48.4%) (table 4).

Participants also reported a desire to engage with the research team about their DPS data and were receptive to the prospect of receiving adherence feedback. Most wanted to be contacted by the research team following detected non-adherence (n=112, 71.3%); however, preferred timing for this outreach varied. When asked when they would want to be informed of a missed PrEP

**Table 2** Perceived usefulness, accuracy and usability of DPS

	Mean (SD)	Minimally N (%)	Moderately N (%)	Extremely N (%)
Perceived usefulness of DPS				
Help me adhere to PrEP	3.1 (2.9)	58 (36.9)	35 (22.3)	64 (40.8)
Hold me accountable for PrEP adherence	3.6 (3.2)	30 (19.1)	36 (22.9)	91 (58.0)
Assist research team in monitoring my PrEP adherence	4.2 (3.8)	8 (5.1)	12 (7.6)	137 (87.3)
Help someone new to taking PrEP adhere to PrEP	3.4 (3.2)	38 (24.2)	35 (22.3)	84 (53.5)
Help me to access information about my past PrEP adherence on my phone	3.9 (3.5)	21 (13.4)	20 (12.7)	88 (56.1)
Perceived accuracy of DPS				
Trust that DPS would accurately provide information on daily PrEP adherence	3.6 (3.3)	18 (11.5)	51 (32.5)	88 (56.1)
System Usability Scale (SUS)				
SUS score	70 (27.5)	–	–	–

Note: Reported means are mean Likert scores.  
DPS, pre-exposure prophylaxis; PrEP, pre-exposure prophylaxis.

dose, half the sample expressed a desire to be contacted after each missed dose (n=87, 55.4%), while a quarter only wanted to be notified if their non-adherence would meaningfully reduce their HIV protection (n=39, 24.8%). When asked whether it would be acceptable for researchers to purposefully not notify them of detected non-adherence events—for example, in the context of clinical trials aimed at developing adherence interventions—participants were divided, with some reporting that this would be extremely (n=57, 36.3%) acceptable, and others reporting that it would be moderately (n=53, 33.8%) and minimally (n=47, 29.9%) acceptable.

#### Data sharing considerations in the context of DPS research

Participants' reported willingness to share DPS data with various stakeholders was mixed. The majority were minimally concerned about the prospect of sharing adherence data with the study principal investigator (n=130, 82.8%) and study team (n=126, 80.3%) (table 5). Most were also

extremely willing to share data with primary care teams or PrEP prescribers (n=109, 69.4%) and with the DPS manufacturer (n=80, 51.0%), as well as with a partner or significant other(s) (n=85, 54.1%). Conversely, when asked about sharing data with casual sex partner(s), the greatest proportion of participants were minimally willing to do so (n=63, 40.1%). Most were also minimally willing to share adherence data with family (n=113, 72.0%), friends (n=101, 64.3%) and insurance companies (n=95, 60.5%) (table 5). Additionally, most participants reported that they would allow the research team to store anonymised PrEP adherence data in a data bank for use by other researchers (n=143, 91.1%).

As for participants' willingness to interact with and share other types of data (ie, beyond PrEP adherence information) in a research context, findings were mixed. Over half (n=94, 59.9%) were extremely willing to interact with an additional wearable device, paired with the DPS,

**Table 3** Willingness and importance of motivations to participate in DPS-based research studies to measure PrEP adherence

	Mean (SD)	Minimally N (%)	Moderately N (%)	Extremely N (%)
Willingness to participate				
Willing to participate in DPS-based study	3.4 (3.2)	43 (27.4)	32 (20.4)	82 (52.2)
Importance of motivations to participate				
Receive money for participation	4.0 (3.6)	18 (11.5)	31 (19.7)	108 (68.8)
Contribute to research efforts	3.9 (3.5)	18 (11.5)	34 (21.7)	105 (66.9)
Gain access to personal PrEP adherence information	3.6 (3.3)	27 (17.2)	38 (24.2)	92 (58.6)
Gain access to free PrEP	3.5 (3.3)	46 (29.3)	20 (12.7)	91 (58.0)
Opportunity to discuss PrEP adherence with study team	3.2 (2.9)	43 (27.4)	51 (32.5)	63 (40.1)

Note: Reported means are mean Likert scores.  
DPS, digital pill systems; PrEP, pre-exposure prophylaxis.

**Table 4** Preferred outreach methods, frequency of data access and perceived usefulness of adherence information from DPS

Preferred outreach method after DPS-detected non-adherence*	N (%)			
Automated text message	125 (79.6)			
Notification within DPS app	101 (64.3)			
Automated phone call reminder	17 (10.8)			
Phone call from study team	22 (14.0)			
Brief text message interactions (<5 min) around PrEP adherence strategies	27 (17.2)			
Text messages with educational information about sexual health and PrEP	20 (12.7)			
Other	3 (1.9)			
No outreach	7 (4.5)			
Preferred frequency for accessing PrEP adherence data	N (%)			
Daily or on-demand	66 (42.0)			
Once a week	52 (33.1)			
Once a month	16 (10.2)			
Only if I miss a dose	18 (11.5)			
No desire to access adherence data	5 (3.2)			
Perceived usefulness of types of adherence information	Mean (SD)	Minimally N (%)	Moderately N (%)	Extremely N (%)
Visual record of all PrEP doses taken (eg, via in-app calendar)†	3.65 (3.3)	29 (18.5)	31 (19.7)	96 (61.1)
Weekly message reporting number of PrEP doses taken (eg, 'You took 5 of 7 PrEP pills this week')	3.61 (3.3)	32 (20.4)	31 (19.7)	93 (59.2)
Weekly message reporting percentage of PrEP doses taken (eg, 'You took 75% of your PrEP pills this week')	3.24 (3.0)	52 (33.1)	29 (18.5)	76 (48.4)

Note: Reported means are mean Likert scores.  
 \*For this question, participants were instructed to select all responses that applied.  
 †N=156 (data unavailable for one participant).  
 DPS, digital pill systems; PrEP, pre-exposure prophylaxis.

that would collect biometric information during PrEP use to better understand the contextual basis of ingestions (online supplemental eTable 3). Half the sample was also extremely willing to interact with text messages (n=79, 50.3%) that would query DPS users about antecedent substance use and sexual activity, as compared with only 28.7% (n=45) who were extremely willing to receive phone calls eliciting the same information. Only some were extremely willing to receive text messages (n=57, 36.3%) or phone calls (n=37, 23.6%) to report general daily activities and location. More than half the sample also reported being either extremely (n=68, 43.3%) or moderately (n=37, 23.6%) willing to share smartphone data (eg, geographic location, battery level, text messaging and frequency of DPS app use) while participating in DPS-based research. A similar percentage was extremely (n=67, 42.7%) or moderately (n=41, 26.1%) willing to provide self-collected blood work (online supplemental eTable 3).

## DISCUSSION

Maintaining adherence to PrEP is particularly difficult for certain populations, including MSM with substance use, and accurate adherence measurement remains a challenge.<sup>8 10 15</sup> DPS enable direct measurement of PrEP adherence and provide a platform by which to understand the context in which adherence and non-adherence occur. DPS adherence data may therefore be used to inform the delivery of real-time adherence interventions. While small studies have demonstrated the feasibility of deploying DPS,<sup>21</sup> this investigation adds larger-scale quantitative data from a national sample of MSM who are behaviourally vulnerable to HIV. Overall, participants in this study were accepting of DPS technology and reported willingness to engage in future DPS-based PrEP adherence research. These data should inform the design of future DPS studies by indicating that first, the DPS is a reasonable technology to deploy in a clinical trial to understand PrEP adherence, and second, that intervention development based on DPS-detected adherence data should be designed with consideration of individuals' perceptions of DPS functionality.

**Table 5** Willingness to share and concern about sharing DPS-detected PrEP adherence data with various stakeholders

	Mean (SD)	Minimally N (%)	Moderately N (%)	Extremely N (%)
<b>Willingness to share adherence data</b>				
Principal investigator	4.1 (3.7)	17 (10.8)	22 (14.0)	118 (75.2)
Entire study team	3.9 (3.6)	22 (14.0)	27 (17.2)	108 (68.8)
Primary care physician or PrEP prescriber	3.9 (3.6)	21 (13.4)	27 (17.2)	109 (69.4)
Family member(s)	2.0 (1.9)	113 (72.0)	21 (13.4)	23 (14.6)
Friend(s)	2.2 (2.2)	101 (64.3)	25 (15.9)	31 (19.7)
Partner or significant other(s)	3.4 (3.2)	48 (30.6)	24 (15.3)	85 (54.1)
Casual sexual partner(s)	2.9 (2.8)	63 (40.1)	35 (22.3)	59 (37.6)
Pharmaceutical company that makes PrEP	3.1 (3.0)	60 (38.2)	32 (20.4)	65 (41.4)
Company that makes the DPS	3.3 (3.2)	52 (33.1)	25 (15.9)	80 (51.0)
All healthcare providers involved in regular care	3.3 (3.1)	53 (33.8)	29 (18.5)	75 (47.8)
Insurance company	2.3 (2.3)	95 (60.5)	22 (14.0)	40 (25.5)
Nurse(s) not involved in the research	2.8 (2.7)	78 (49.7)	21 (13.4)	58 (36.9)
Pharmacist(s) not involved in the research	2.7 (2.6)	82 (52.2)	26 (16.6)	49 (31.2)
Public health organisation or agency	3.2 (2.0)	59 (37.6)	30 (19.1)	68 (43.3)
Company that makes smartphone application	2.9 (2.8)	70 (44.6)	23 (14.6)	64 (40.8)
<b>Concern about sharing adherence data</b>				
Principal investigator	1.6 (1.5)	130 (82.8)	12 (7.6)	15 (9.6)
Entire study team	1.7 (1.6)	126 (80.3)	16 (10.2)	15 (9.6)
Primary care physician or PrEP prescriber	1.8 (1.8)	127 (80.9)	9 (5.7)	21 (13.4)
Family member(s)	3.4 (3.2)	57 (36.3)	22 (14.0)	78 (49.7)
Friend(s)	3.2 (3.1)	62 (39.5)	24 (15.3)	71 (45.2)
Partner or significant other(s)	2.3 (2.3)	100 (63.7)	19 (12.1)	38 (24.2)
Casual sexual partner(s)	2.7 (2.6)	78 (49.7)	30 (19.1)	49 (31.2)
Pharmaceutical company that makes PrEP	2.4 (2.4)	96 (61.1)	17 (10.8)	44 (28.0)
Company that makes the DPS	2.4 (2.3)	97 (61.8)	21 (13.4)	39 (24.8)
All healthcare providers involved in regular care	2.2 (2.1)	110 (70.1)	15 (9.6)	32 (20.4)
Insurance company	3.3 (3.1)	55 (35.0)	33 (21.0)	69 (43.9)
Nurse(s) not involved in the research	2.7 (2.6)	82 (52.2)	28 (17.8)	47 (29.9)
Pharmacist(s) not involved in the research	2.7 (2.7)	80 (51.0)	24 (15.3)	53 (33.8)
Public health organisation or agency	2.4 (2.3)	99 (63.1)	22 (14.0)	36 (22.9)
Company that makes smartphone application	2.6 (2.6)	92 (58.6)	17 (10.8)	48 (30.6)

Note: Reported means are mean Likert scores.

DPS, digital pill systems; PrEP, pre-exposure prophylaxis.

Our nationwide sample was composed of adult, HIV-negative MSM on PrEP who were sexually active, had significant substance use, reported worrying about daily PrEP adherence, and, importantly, had not previously participated in biomedical PrEP or substance use research studies. Despite reported concerns about missing PrEP doses, participants were well engaged in medical care, as evidenced by frequent HIV testing, and were PrEP adherent per self-report. Participants' acceptance of DPS technology to measure PrEP ingestion patterns was high, as was interest in participating in research using DPS. Participants also indicated that they would trust

the adherence data detected and reported by the DPS, though it remains unclear whether this perception would differ in the DPS context as compared with other tools for adherence measurement (eg, Bluetooth-enabled smart pill bottles); moreover, further research is needed to better understand the extent to which participants perceive differences between data generated by different adherence technologies. Importantly, those with frequent substance use before or during sexual activity were more amenable to participating in DPS-based research. Less than half the sample (40.8%) reported that DPS would be extremely useful for maintaining PrEP adherence, which



suggests that DPS use alone may not produce a Hawthorne effect<sup>31</sup> as previously postulated, perhaps due to its similarities to existing pill-taking routines (eg, digital pills are stored in a bottle vs another device, and ingested in the same manner as standard pills). This finding is consistent with our prior qualitative work, which indicated that MSM on PrEP may not view the DPS as an adherence intervention, but as a measurement tool.<sup>21</sup> This distinction will be critical for intervention development and efficacy studies that integrate the DPS to collect adherence data.

The use of DPS in both research and future clinical care settings could fundamentally change ethical obligations surrounding adherence reporting and support, especially in the context of pharmacotherapy, such as PrEP, in which missed doses may result in waning HIV protection. In contrast to indirect measures of adherence, such as Bluetooth-enabled smart pill bottles, the DPS directly confirms the presence of medication, which could alter the way in which institutional ethics review boards view the acquisition and interpretation of the data. Our findings demonstrate that there continues to be discordance surrounding notification preferences after PrEP non-adherence. Participants recognised that DPS technology records adherence data in real time, and perceived a responsibility on the part of research teams to alert users of detected non-adherence (n=100, 63.7% reported that it would be minimally or moderately acceptable for research teams *not* to alert DPS users of non-adherence). However, participants were divided on the optimal timing for such notifications, with approximately half wanting to be contacted after each missed dose (n=87, 55.4%), and a quarter wanting to be contacted only if their non-adherence meaningfully reduced their HIV protection (n=39, 24.8%). Providing participants with the ability to customise the frequency of outreach notifications connected to the DPS may be one option for addressing this diversity of preferences related to non-adherence notifications.

These findings speak to a larger ethical question surrounding the return of adherence information to DPS users, particularly when such information is actionable. Previous ethical frameworks around adherence measurements suggest four strategies for providing adherence data to research participants—ranging from informed consent, in which the adherence technology and intent is discussed in detail with participants, to complete blinding of participants to the adherence tool in use.<sup>32</sup> In certain contexts, it may be in researchers' interest to observe non-adherence without intervening—for example, in PrEP adherence intervention development studies with suboptimally adherent individuals—in order to measure the effectiveness of a particular intervention; however, this may place participants at risk if they erroneously assume that they will be informed of all non-adherent events. In addition, not discussing the adherence system in use and/or withholding adherence data that could lead to significant health outcomes (eg, in the context of PrEP adherence, possible HIV acquisition) could negatively impact

participant autonomy.<sup>33</sup> In one prior DPS-based study in this population, we informed participants during consent that feedback would be provided if non-adherence patterns suggested waning HIV protection.<sup>20</sup> In a separate study, we informed participants during consent, and throughout the study, that, if randomised to the control arm (involving DPS use alone with no intervention), feedback would not be provided.<sup>34</sup> Data from this study reaffirm this approach—that is, providing participants with clear information on enrolment surrounding the frequency of DPS data query, as well as the algorithmic actions that occur if non-adherence is detected, in order to reduce potential misconceptions around expected feedback.

Studies that do not plan to notify participants of non-adherence must ensure that participants are sufficiently scientifically literate to understand the implications of PrEP non-adherence for their health and HIV status, and should confirm their understanding that no adherence feedback will be provided. In intervention studies in which investigators do notify participants of adherence changes that may result in disease progression or acquisition, actionable data must be provided in plain language to maximise comprehension. Such notification events may be analysed as covariates in order to evaluate their contribution to intervention efficacy. Both the frequency with which the researchers plan to assess participants' adherence data during the study, and any interventions surrounding non-adherence that may be medically necessary to implement, should be clearly communicated to participants during informed consent.<sup>35</sup> This study indicates that these are key data points likely to impact willingness to enrol in DPS-based studies—and that clarity during informed consent on procedures relevant to these motivations is essential to ensuring adequate participant protections and limiting confusion. Overall, user education will be crucial to the ethical implementation of DPS technology both in research and ultimately in clinical care.

This study had several limitations. First, participants were enrolled through Grindr, a popular social media networking site. The sample may, therefore, be biased towards individuals who own a smartphone, as well as those who are already comfortable both using technology and sharing information via technology. Additionally, users of dating apps have been previously described to have higher risk behaviour profiles and are more likely to test positive for a sexually transmitted infection, as well as more likely to be on PrEP, than non-users.<sup>36 37</sup> The socio-demographic characteristics, technological fluency and willingness to participate in technology-based research among individuals in this study may not be generalisable to MSM overall. Second, participants were mostly non-Hispanic/Latinx, white individuals, engaged in sexual healthcare, with GBMMS scores that suggested trust in medical and research settings; as such, MSM of colour—who report greater medical mistrust as a result of systematic discrimination and historical wrongdoings

by the medical community<sup>38–40</sup>—and MSM not engaged in care may represent the populations most in need of PrEP support and adherence interventions. Acceptance of DPS technology may additionally vary across other sociodemographic characteristics that have been historically distrustful of medical and research establishments. The results may not be as generalisable to non-white individuals, those with more severe substance use, or those who are not engaged with smartphone or technology use. Third, we do not have surveillance data on MSM who are on PrEP, use substances and use Grindr; as such, we are unable to assess the extent to which our sample reflects this broader group or to weight our analyses. Finally, the study variables were all based on self-report and are vulnerable to the biases of that methodology.

Despite these limitations, our results suggest that, for future investigations exploring oral PrEP adherence in individuals with substance use, the DPS may be a reasonable adherence measurement tool to deploy in both a research and clinical care context. Even in light of compelling data surrounding the efficacy of long-acting, injectable formulations of PrEP,<sup>41</sup> the DPS and other oral adherence measurement tools remain highly relevant given the challenges individuals may experience in accessing injectable PrEP, the lack of availability of injectable PrEP for certain populations (eg, internationally and among underserved patient groups who may be most in need of adherence support), and current uncertainty surrounding how best to deploy injectable PrEP among individuals with substance use disorders. Additionally, previous work has demonstrated that populations that may qualify for injectable PrEP also desire choice between injectable and oral versions of PrEP.<sup>42</sup> The DPS, therefore, provides an option for individuals who may remain interested in oral PrEP, as well as in contexts in which the infrastructure to support injectable PrEP delivery is unavailable or where oral PrEP is required to bridge gaps in the use of injectable PrEP.

## CONCLUSIONS

Overall, this investigation demonstrates that MSM on PrEP who are at greater adherence risk due to substance use, especially before and during sex, reported willingness to participate in future DPS-related PrEP adherence research. The perceived usefulness of DPS for increasing accountability for PrEP adherence was mixed, but participants reported a high degree of trust in the system to accurately measure adherence. These findings have key bioethical implications that will inform the design of future DPS-based studies, primarily surrounding the mechanisms, timing and obligations for notification following DPS-detected non-adherence. While adherence intervention studies may benefit from integration of DPS for accurate and direct measurement of real-time adherence, the implications of observing users' ingestion patterns as they occur must be carefully considered—and the risks of non-adherence and

potential ethical obligations for non-adherence counselling, especially in formative pilot work, should be balanced with the need to measure the efficacy of novel interventions.

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