A Pilot Trial of a Smartphone-Based Contingency Management Intervention to Improve Pre-Exposure Prophylaxis (PrEP) Adherence

John T. Mitchell, Ph.D., 1,2* Sara LeGrand, Ph.D., 3 Lisa B. Hightow-Weidman, M.D., 4 Mehri S. McKellar, M.D., 5 Angela D.M. Kashuba, Pharm. D., 6 Mackenzie Cottrell, Pharm. D., 6 Tony McLaurin, MSPH, 1 Goutam Satapathy, Ph.D., 7 & F. Joseph McClernon, Ph.D. 1,2

1 Department of Psychiatry & Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, United States of America.
2 Duke Center for Addiction Science and Technology, Durham, North Carolina, United States of America.
3 Duke Global Health Institute, Duke University, Durham, North Carolina, United States of America.
4 Institute of Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America.
5 Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina, United States of America.
6 Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America.
7 Intelligent Automation Incorporated, Rockville, Maryland, United States of America.

*Contact Information: John T. Mitchell, Ph.D.; Department of Psychiatry & Behavioral Sciences; Duke University Medical Center; 2608 Erwin Road; Pavilion East; Suite 300; Durham, NC, 27705; Phone 919-681-0012; FAX 919-681-0016; john.mitchell@duke.edu.
Abstract

**Background**: Pre-exposure prophylaxis (PrEP) provides a strong preventative benefit to individuals at-risk for HIV. While PrEP adherence is highly correlated with its efficacy, adherence rates are variable both across and within persons. **Objective**: The objective of this study was to develop and pilot test a smartphone-based intervention, called mSMART, that targets PrEP adherence. mSMART provides contingency management (CM) in the form of monetary incentives for daily PrEP adherence based on a real-time adherence assessment using a camera-based medication event-monitoring tool, as well as medication reminders, PrEP education, individualized behavioral strategies to address PrEP adherence barriers, and medication adherence feedback. **Methods**: This was a four-week open-label, phase I trial in a community sample of young men who have sex with men already on PrEP (n = 10). **Results**: While adherence composite scores corresponding to PrEP biomarkers indicated 90% of the sample already had an acceptable baseline adherence in the protective range, by the end of the four-week period scores improved for 30% of the sample—adherence did not worsen for any participants. Participants reported mean PrEP adherence rates of 91% via daily entries in mSMART. At the end of the four-week period, participants indicated acceptable ratings of satisfaction, usability, and willingness to recommend mSMART to others. **Conclusion**: This research is the first to apply CM to PrEP adherence. Findings indicated that mSMART is feasible and acceptable. Such an adherence intervention administered via a user-friendly smartphone application can allow for widespread dissemination. Future efficacy trials are needed.

**Trial Registration**: ClinicalTrials.gov [NCT02895893](https://clinicaltrials.gov/ct2/show/NCT02895893)
Introduction

Pre-exposure prophylaxis (PrEP) in the form of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) is a highly effective tool to prevent HIV infection [1-9]. However, adherence rates to this once-daily medication are highly variable in clinical trials, ranging from 12% to 82% [4, 10-15]. This is particularly significant for HIV prevention since the effectiveness of oral PrEP is strongly associated with sustained adherence [3, 4, 16]. For example, among those receiving PrEP in a 72-week open-label extension trial, HIV incidence significantly dropped from 4.7 infections per 100 person-years if the drug was not detected in blood to 2.3, 0.6, and 0.0 infections per year if blood levels correlated with participants taking less than two tablets per week, two to three tablets per week, and four or more tablets per week, respectively [3]. Young men who have sex with men (MSM) are at-risk for HIV and could therefore benefit from PrEP. MSM represent just 2% of the United States (US) population but account for 67% of all new HIV diagnoses, which is driven in part by increased rates in young MSM [17]. In conjunction with trials indicating that younger participants, including MSM, are less likely to be adequately adherent to PrEP [3, 18, 19], interventions that target PrEP adherence are needed.

Despite the importance of PrEP adherence, there are few empirically-supported interventions targeting adherence. One pilot trial indicated that a cognitive-behavioral intervention including four to six face-to-face sessions improved PrEP adherence among MSM in comparison to a time-matched control intervention [20]. While such interventions are promising, easily disseminated and wide-reaching interventions that maintain fidelity to rigorous intervention protocols may further enhance efforts to promote PrEP adherence. Smartphones offer such a platform for personalized and flexible interventions to improve health outcomes that can be administered in a uniform and user-friendly format [21]. Smartphones are used by an increasing segment of the US population (e.g., 77% owned one in 2016, up from 35% in 2011) [22]—people who carry smartphones generally have them within reach and on at all times [23]. However, despite the fact that there are over 800 medication adherence applications for a range of conditions, few have been widely studied [24]. Although some research is beginning to investigate use of daily text messaging to support PrEP adherence [25], a smartphone application targeting HIV prevention that includes PrEP screening [26], a smartphone application that incorporates PrEP adherence among MSM in an ongoing trial [27], to our knowledge there are no published studies on medication adherence smartphone applications for PrEP.

Contingency management (CM), administered via smartphones, may be a promising intervention approach for improving PrEP adherence. CM is a behavioral intervention that uses systematic reinforcement dependent on the occurrence of a specific behavior and is effective in improving adherence to medications for a range of medical and psychiatric conditions [28]. CM has been used to successfully improve adherence to antiretroviral medications among HIV-positive and HIV-exposed individuals [29, 30], but has yet to be examined as an intervention for PrEP adherence.

The aim of this study was to develop and pilot test a smartphone-based CM intervention, called mSMART, that targets PrEP adherence. In addition to CM, mSMART provides medication
reminders, PrEP education, individualized behavioral strategies to address PrEP adherence barriers, and medication adherence feedback. mSMART also assesses adherence in real-time using a camera-based medication event-monitoring tool. This was a four-week open-label, phase I trial. We examined the feasibility and acceptability of mSMART in a sample of young MSM prescribed PrEP in a community setting.

Methods

Participants

Inclusion criteria included: male sex at birth, age 18-30 years, self-report having sex with men in the last six months, self-report currently prescribed and taking PrEP for HIV prevention, English speaking, and own an Android or iPhone compatible with the mSMART smartphone application. Exclusion criteria included significant medical or psychiatric conditions that may interfere with study participation (e.g., suicidality) or being unable to attend both study visits. There were no inclusion/exclusion criteria pertaining to amount of time participants were prescribed PrEP prior to enrollment. Participants were recruited via community advertisements and word-of-mouth.

Twenty-seven screens conducted over the phone were held and 14 individuals were invited for the baseline assessment. Individuals were not invited for a baseline visit for the following reasons: they did not respond to phone messages \( (n = 2) \), did not meet age inclusion criterion \( (n = 5) \), were not currently prescribed PrEP \( (n = 1) \), self-reported HIV positive status \( (n = 1) \), did not live close enough to attend laboratory visits \( (n = 1) \), and were not male \( (n = 1) \). Among the 14 invited for a baseline visit, 2 participants did not attend the visit. A total of 12 participants were enrolled, but 10 participants were included in the current analysis—2 participants had baseline TVF/TFV-DP levels indicating that they were not taking PrEP at baseline or follow-up (see Figure 1).
Procedures and Measures

Two laboratory visits were required: baseline and follow-up. Participants were provided the mSMART smartphone application on their smartphone and asked to use it daily during the four-week period between visits.

**Baseline visit.** Following informed consent, participant demographic, medication, and medical/psychiatric history information were collected in paper-and-pencil format to characterize the sample. Additional questionnaires were administered via a web-based survey tool during the
visit to further characterize the sample. The 6-item Risk Behavior Assessment for MSM [31] recommended by the Centers for Disease Control and Prevention (CDC) [32, 33] was administered to assess HIV risk over the past six months. The 9-item Patient Health Questionnaire-9 [34] assessed depressed mood over the past two weeks. Substance use was assessed with the 10-item Drug Abuse Screening Test [35] and the 10-item Alcohol Use Disorders Identification Test [36]. The number of perceived barriers to PrEP adherence was assessed with the 20-item Adherence Starts with Knowledge questionnaire (ASK-20) [37]—the original version of this scale was modified to inquire about PrEP specifically. This measure was used to characterize perceived PrEP adherence barriers at baseline, as well as an outcome measure to compare with follow-up visit ratings.

A blood draw was also conducted to assess for biomarkers of PrEP adherence at baseline. Blood samples were collected to assess concentrations of tenofovir (TFV) in plasma and intracellular TFV-diphosphate (TFV-DP) in upper layer packed cells to both characterize baseline levels and as a comparison with the follow-up assessment levels using methods previously described in Adams et al. [38]. These levels were used to develop a semi-ordinal composite adherence score over the past four weeks ranging from 0 (low/no doses of drug identified: no detectable TFV and <10,000 fmol/mL TFV-DP) to 5 (good adherence: >10ng/mL TFV and >1,000,000 fmol/mL TFV-DP) [15]. A score of 4 (i.e., four to five doses per week) or 5 (approximately daily dosing) is typically considered the level of adherence in which PrEP is efficacious among MSM [39].

At the conclusion of the baseline visit, study participants were registered with the mSMART application by the study team on a secure website [40] and the application was downloaded by participants from the appropriate application distribution platform for their operative system (e.g., Apple Store, Google Play). Participants received brief instructions from an experimenter on the functions of mSMART. Overall, the baseline visit took approximately 90-120 minutes to complete.

**Follow-up visit.** The blood draw to assess for TFV/TFV-DP was repeated and the ASK-20 questionnaire modified for PrEP was re-administered. Treatment acceptability ratings were provided by participants based on responses to individual items examining overall satisfaction with mSMART (i.e., “What was your overall satisfaction with mSMART?”), mSMART usability on a daily basis (i.e., “How usable was mSMART on a daily basis?”), difficulty learning how to use mSMART (i.e., “How difficult was it to learn how to use mSMART?”), willingness to recommend mSMART to others (i.e., “Would you recommend mSMART to a friend who is taking a medication?”), and overall user-friendliness of mSMART (i.e., “How user-friendly was mSMART?”) on a Likert scale ranging from 1 (not at all) to 4 (extremely). These items were administered in an in-person interview format and were adapted from our past use of a similar scale [41]. The System Usability Scale (SUS) [42] was administered via a web-based survey tool as a measure of treatment acceptability. The SUS is a 10-item scale that assesses responses on a 5-point Likert scale with scores ranging from 0 to 100. Semi-structured exit interviews were also conducted for qualitative analysis of participant experiences and perceptions of mSMART. Interview questions addressed topics such as mSMART design features, navigation, barriers to use, and features that facilitated regular use similar to other studies examining participant experience with smartphone-based interventions (e.g., [43]).
Participants also completed pre-determined tasks within the smartphone application during the follow-up study visit following guidelines from another smartphone application development study [43]. An experimenter sat next to the participant, provided instructions on six different tasks, and recorded the time to complete each task. These six tasks involved: (a) taking a picture of their medication, (b) changing the reminder time for daily dosing, (c) checking how much money was earned using the smartphone application, (d) checking for any questions prompted by mSMART, (e) looking up a detail about medication side effects, and (f) looking up a second detail about medication side effects. The time recorded for each task was based on the first attempt to complete it.

**mSMART intervention.** mSMART was used by participants over a four-week period between the baseline and follow-up visits. mSMART is composed of six different components (see Figure 2) that target medication adherence.

The development of mSMART was conducted through a multistage process initially as a smartphone application for medication adherence for cigarette smokers during quit attempts [44]. It was adapted for the current study for PrEP and is the first administration of mSMART to a sample prescribed PrEP. The adaptation of mSMART for PrEP was informed by studies of adherence barriers in PrEP trials (e.g., [45-48]) and feedback from experts working with and developing interventions for individuals at risk for HIV. The Information, Motivation, and Behavioral skills (IMB) model [49], which conceptualizes health behavior change as a product of mediators including information about the behavior, motivation to change, and behavioral skills, guided the refinement of mSMART for PrEP. The IMB model has been used to guide the development of numerous HIV prevention interventions (e.g., [50]).
The first mSMART component was Medication Aide. This component of mSMART included the CM procedures. Upon receiving their daily PrEP reminder notification, participants touched the Medication Aide icon and were then directed to enter either a dose of PrEP that they (a) were about to take or (b) had already taken. If a participant indicated that he was about to take his daily PrEP dose, the camera-based medication event-monitoring tool was activated. This involved taking the participant to another screen that prompted him to touch a pill icon that would then open up the camera feature of their phone. The mSMART application would automatically take a picture and would take approximately 5-10 seconds to focus on the pill the participant was holding in his hand—a feedback bar indicating progress was provided over the top portion of the picture. For this study, these pictures were not examined by the study team or saved, although mSMART has that capability. If participants had already taken their daily dose of PrEP, they would manually enter when they took their daily dose of PrEP. In either case, as long as participants reported taking their daily dose of PrEP within two hours of their predetermined dosing time each day (dosing times were selected by participants), they received reinforcement. A fixed-ratio schedule of reinforcement was adopted. Participants received feedback that they earned $2 every time they logged a dose (whether using the camera feature or manually) as long as it was within a two-hour window of the time they listed as their daily dosing. Feedback about money earned upon taking their daily dose of PrEP was provided immediately by mSMART. Over the four-week period, participants could earn up to $56. Participants could opt to receive the money that they earned in accordance with the CM procedures weekly or at the end of the four-week intervention period.

The second mSMART component was SMART Desk. This component was an interactive space where mSMART prompted brief daily surveys (i.e., one to four questions per day pertaining to knowledge or concerns about PrEP, knowledge about HIV, and general medication use concerns or problems). These questions were phased out after any seven day window only if participants were achieving 100% adherence with logging daily PrEP doses in that window, but were resumed if a dose was not logged. For participants who were not logging all daily PrEP doses, they continued to receive daily questions from the SMART Desk. Notifications informing participants of missing a PrEP dose were also provided through the SMART Desk.

The third mSMART component was Adherence Strategies. This component described behavioral strategies to address PrEP adherence barriers identified in the literature [45-48]. These strategies were prioritized in list form based on responses in the SMART Desk and could be accessed at any time by clicking on the Adherence Strategies icon. For example, if a participant indicated he does not have difficulty remembering to take daily PrEP doses but had a relatively poor understanding of how PrEP prevents HIV on previous SMART Desk questions, then the Adherence Strategies would present educational information about how PrEP prevents HIV before presenting behavioral strategies to help the participant remember to take his medication. Thus, adherence strategies were individualized based on participant responses in the SMART Desk. In addition to accessing adherence strategies by clicking on the Adherence Strategies icon, participants were automatically routed to specific Adherence Strategies from the SMART Desk after completing questions in the SMART Desk. For example, if the SMART Desk asked about remembering to take medication, the participant would be routed to a strategy within Adherence Strategies to address medication forgetfulness. This routing occurred regardless of the response
selected with the intent to increase exposure to a variety of adherence strategies, which was balanced against personalized presentation of strategies based on SMART Desk responses described above.

The **fourth mSMART component** was Coping Strategies and listed common PrEP side effects. Participants could access a list of side effects at any time and click on any to view strategies to mitigate them. The most common side effects reported in the literature (e.g., upset stomach, headache, vomiting [32, 33]) were included.

The **fifth mSMART component** was Prescription and Doses, which is where participants set up their preferred time to receive medication reminders. Participants could change this setting at any time and therefore could modify it on days they anticipated taking PrEP at a different time.

The **sixth mSMART component** was Treatment Progress. This feature provided feedback about the participant’s overall PrEP adherence in the form of percentage of days they logged a dose (within the two hour window) within the Medication Aide feature. Participants could also click on this feature to see how much money they had earned based on the CM procedures.

Data Analysis

**Adherence outcomes.** Perceived and objective PrEP adherence outcomes were assessed via change scores on the ASK-20 and medication adherence scores based on TVF/TFV-DP, respectively.

**Treatment feasibility.** Feasibility was assessed in the following ways: study attrition rate and any smartphone-mSMART compatibility incidents, daily engagement with mSMART, time needed to completed the pre-determined tasks on mSMART, and number of prompts (initiated by either participant or experimenter) to assist participants in completing the tasks.

**Treatment acceptability.** Acceptability was assessed in multiple ways. First, responses to individual treatment acceptability questions about mSMART (i.e., overall satisfaction, usability on a daily basis, difficulty learning mSMART, willingness to recommend mSMART to others, and overall user-friendliness) were descriptively analyzed. Second, SUS scores at or above 68 were considered acceptable [51]. Third, we considered responses to semi-structured exit interviews for qualitative analysis. Interviews were digitally recorded, transcribed, and qualitatively analyzed. Qualitative analysis involved identification of themes that emerged from participant interviews. These themes were identified through an iterative process following procedures similar to our past qualitative analysis approach [52, 53]. That is, an initial list of anticipated themes based on the study team’s experience with mSMART in other populations and separate experience with young MSM (e.g., liking and disliking different features of mSMART). These themes were subsequently refined based on one of the author’s experience conducting the exit interviews and reading all interview transcripts (e.g., features that participant’s would like to see changed). Another rater then read through the transcripts to comment on the theme descriptions and identify any additional themes not previously considered. Next, both raters identified any discrepancies in theme identification and finalized the themes. Following this process, the two raters separately read through the transcripts (n = 6 per rater) in a MS Word...
document and identified theme endorsements for each participant. Each interview excerpt that was identified with a theme endorsement was transferred to an Excel document so that frequency counts for particular themes could be summed across the full sample. We have adopted similar procedures in past studies [52]. Inter-rater reliability between raters was assessed on a subset of interview excerpts. Kappa coefficient between raters was .90 when determining if a theme should be endorsed.

Results

Sample Characteristics

The sample was composed of 10 young MSM currently prescribed PrEP in the community. The sample was predominantly White (70%) and highly educated (70% earned at least an undergraduate degree). The average number of months on PrEP was 8.30 with use ranging from 0.5 to 12 months. All but one participant reported being on PrEP for at least 5 months. The entire sample exceeded the MSM Risk Index Score of 10 used to evaluate appropriateness for PrEP [32, 33], indicating high risk for HIV. In addition, participants yielded low scores for depressed mood, drug use, and alcohol use (see Table 1 for a summary).

<table>
<thead>
<tr>
<th>Table 1. Sample characteristics (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Multiracial</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Not Hispanic</td>
</tr>
<tr>
<td>Not Reported</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>High School Graduate</td>
</tr>
<tr>
<td>Partial College</td>
</tr>
<tr>
<td>College Graduate</td>
</tr>
<tr>
<td>Postgraduate Studies</td>
</tr>
<tr>
<td>Employment status</td>
</tr>
<tr>
<td>Full-Time</td>
</tr>
<tr>
<td>Part-Time</td>
</tr>
<tr>
<td>Assistance</td>
</tr>
<tr>
<td>Unemployed</td>
</tr>
<tr>
<td>Dependent or Student</td>
</tr>
</tbody>
</table>
Not reported 1 (10)
Salary Range
$0-$10,000 3 (30)
$10,000-$25,000 3 (30)
$25,000-$50,000 0 (0)
$50,000-$75,000 2 (20)
>$75,000 1 (10)
Not Reported 1 (10)
Months Prescribed PrEP 8.30 (3.45)
MSM Risk Index Score$ 21.50 (5.48)
Smartphone
iPhone 9 (90)
Android 1 (10)
PHQ9
Minimal depression (scores 0-5) 9 (90)
Mild depression (score = 6) 1 (10)
DAST
None 7 (70)
Low 3 (30)
AUDIT
Low risk 10 (100)

Notes. *100% of the sample exceeded the cut-off score of 10 and therefore are recommended to evaluate for PrEP per Center for Disease Control and Prevention guidelines [32, 33]. Patient Health Questionnaire-9 = PHQ-9; DAST = Drug Abuse Screening Test; AUDIT = Alcohol Use Disorders Identification Test.

Adherence Outcomes

**Objective Adherence.** PrEP composite adherence scores based on TFV/TFV-DP values indicated that PrEP adherence increased for 30% of the sample (n = 3) and did not change for 70% of the sample (n = 7). For participants that did not indicate any change, PrEP adherence scores were already at a level considered efficacious (i.e., ≥ 4 doses per week) at baseline. Among the three participants whose PrEP adherence scores increased, one had a baseline score below what is considered efficacious. No PrEP composite adherence scores decreased. Table 2 provides baseline and follow-up scores.

**Table 2. Frequency of PrEP Composite Adherence Scores at Study Baseline and Follow-Up Visits**

<table>
<thead>
<tr>
<th>Composite Score</th>
<th>Baseline (%)</th>
<th>Follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4</td>
<td>8 (80)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>5</td>
<td>1 (10)</td>
<td>3 (30)</td>
</tr>
</tbody>
</table>
Notes. Composite scores were based on concentrations of tenofovir (TFV) in plasma and intracellular TFV-diphosphate (TFV-DP) in upper layer packed cells. Scores assess adherence in the past four weeks ranging from 0 (low/no doses of drug identified) to 5 (good adherence). A score of 4 (i.e., four to five doses per week) or 5 (approximately daily dosing) is typically considered a good level of adherence in which PrEP is efficacious. Since one participant was on PrEP for only two weeks, the baseline visit adherence score for this participant could have been artificially lower as a result of taking PrEP for a shorter duration in comparison to other study participants (i.e., all other participants reported being on it for at least five months). However, this participant yielded a baseline adherence score of 4 indicating an adequate level of protection since starting on PrEP and that his score was likely not artificially lower.

Perceived Adherence. The perceived number of barriers to PrEP adherence was measured with the modified ASK-20 at baseline and follow-up. A comparison of scores within participants indicated an increase in the number of perceived barriers for one participant. This participant indicated on an ASK-20 item that his belief that PrEP was helpful in reaching his overall health goals had decreased. However, three participants indicated that the number of barriers they perceived to PrEP adherence decreased, including barriers associated with the financial cost of PrEP. There was no change in modified ASK-20 scores for 50% of the sample ($n = 5$). One participant did not complete the modified ASK-20 at follow-up.

Treatment Feasibility

There was 0% study attrition. Further, there were no smartphone-mSMART compatibility events in which the mSMART application was not able to function on a study participant’s phone. In terms of daily engagement with mSMART, participants logged a PrEP dose in mSMART (using either the camera-based medication event-monitoring tool or manual entry option) 91% of the time over the four-week intervention period (Figure 3a) with the mean amount earned per CM guidelines of $53 per participant. Among these logged doses in mSMART, 88% involved use of the camera-based medication event-monitoring tool (Figure 3b). Overall, 40% of the sample did not miss any days logging a PrEP dose in mSMART. An additional 40% did not log a PrEP dose in mSMART between one and five days while in the study. Among the remaining participants, one did not log a PrEP dose for six days and the other did not log a PrEP dose for 12 days. Further, 70% of the sample responded to all of the mSMART daily surveys.
Among the six pre-determined tasks on mSMART, all participants were able to complete each task without any prompts (initiated by either participant or experimenter). The amount of time it took to complete these tasks was 5.39 seconds (average across all tasks; see Supplement A).

Treatment Acceptance: Quantitative Analysis
In-person interview items at the follow-up visit indicated that the mean rating (on a scale of 1 [not at all] to 4 [extremely]) for overall satisfaction with mSMART was 2.80 (SD = .63), mSMART usability on a daily basis was 3.50 (SD = .53), willingness to recommend mSMART to others prescribed PrEP was 2.70 (SD = .82), and user friendliness of mSMART was 2.80 (SD = .79). Participants also indicated that difficulty learning how to use mSMART was 1.20 (SD = .42).

On the SUS with total scores ranging from 0 to 100, the mean score was 68.25 (SD = 15.10). Using a score of ≥ 68 as an indicator of mSMART user acceptability, 60% of the sample (n = 6) met this cut-off.

Treatment Acceptance: Qualitative Analysis

Six themes emerged pertaining to: (a) mSMART features that were liked or disliked; (b) daily mSMART use; (c) mSMART aesthetics; (d) learning how to use mSMART; (e) mSMART features that should be added; and (f) the likelihood of using mSMART. The first four themes were further subdivided into comments that were either positive or negative feedback about mSMART (see Supplement B for a summary of endorsement rates across themes).

**mSMART Features: Liked and Disliked.** The majority of the sample, 80%, commented on features that they both liked and disliked—the other 20% commented only on features that they liked and did not report any dislikes. Particular mSMART features that were most frequently mentioned included: using the camera feature (50% liked, 20% disliked, 20% both liked and disliked, 10% did not comment on this feature), receiving daily questions (50% liked, 0% disliked, 30% both liked and disliked, 20% did not comment on this feature), and receiving medication reminders (50% liked, 10% disliked, 10% both liked and disliked, 30% did not comment on this feature). For example, when asked about his overall impression of mSMART, one participant responded in the following way about the medication reminders:

> I think [mSMART] is helpful, I mean, because it also offers some useful information on Truvada and, uhh, the most important thing is it offers reminders and I mean, at least for now, I still need the reminder to remind me to take my medication. Before I started using this app … it’s really easy to forget every day.

Another participant commented on how the daily questions from the SMART Desk were helpful:

> [mSMART] figured out what I struggled with by the questions

Although some participants indicated that they both liked and disliked the camera feature, most comments about disliking the camera feature actually involved initial difficulty learning how to use this feature. For example, one participant stated:

> I think there were like, especially in the first week, there were four or five times I would try to take a picture of the pill and it went straight to uhhh, it wouldn’t, it didn’t read it. And mainly it was times when I was taking the picture and it was too dark, right? I was just like in my room in the morning and didn’t have any lights on, or in our kitchen and it was just really dark. And that was frustrating. Umm, it wasn’t so, I mean it was a minor inconvenience in the grand scheme of the world, right?

After describing this initial experience with the camera feature, this participant went on to say:

> Personally, I definitely think that taking a photo was good.
Other participants indicated that the camera feature helped with consolidating memories to increase confidence that they took their medication. For example:

… using the camera like, really forced me to use it and kind of was a mental check guard for myself to make sure I took the medication … Like I was telling you that, I’m like, did I take the pill? Was it yesterday when I was going to work? Or was that today? And so [inaudible] taking the picture at 5:37, like I did do it today. So I’m not confused. I know when I took it, and that was today.

The money earned in accordance with the CM procedures was not among the mSMART features that participants appeared to find helpful. That is, only 40% indicated liking the CM payment feature of mSMART—20% said it was not a helpful feature in adhering to PrEP and another 40% indicated that they neither liked nor disliked this feature.

Daily use: Facilitators and Barriers. Forty percent of the sample commented on factors that facilitated successful daily use of mSMART, while 60% of the sample commented on factors that both facilitated mSMART use and barriers to mSMART use. The most frequently endorsed factor facilitating daily mSMART use (70%) was using it at the time they received a medication reminder. For example, one participant stated:

I pretty much only used it when I needed to log my, umm, medication, which was at night. Regarding barriers to daily use, the most frequently identified feature was that the speed of mSMART was too slow (i.e., time to transition from one screen to the next or to perform a function) and was therefore a barrier to use (20%):

So, sometimes when you click on the medic—-, like the camera function, it takes a second and then it’ll go, umm, and then it’ll take a minute to get to the next slide and the next screen or whatever you want to call it, which is fine, but I’m just saying like for someone who is going to use it every day and does not have the incentive of here’s … money at the end of the trial, you know what I mean? It could be, people could, someone might get frustrated.

mSMART aesthetics: Liked and Disliked. An equal proportion of participants either commented that they disliked mSMART aesthetics (40%) or both liked and disliked aesthetics of the application (40%)—the other 20% commented either only on aesthetics that they liked (n = 1) or did not comment about aesthetics at all (n = 1). The most frequently identified aesthetic that was disliked was how the content was displayed in text format (70%). For example:

I would go to some of the coping strategies just to like look through them, and I would say, like, you open it, and there’s kind of just a large block of text—that might be a little intimidating. … on the one hand I thought it was helpful because it felt like a pretty clinical tone, umm, like from a healthcare provider, like in a good way. Like, if that’s what you want, you know, if you want that … But, then sometimes I was thinking that maybe I would want a more just like a friend …

The most frequently identified aesthetics that was liked was the overall design of mSMART (40%). For example:

I thought it was pretty well-designed. And, I guess, yeah, I mean it was clearly laid out to me. Umm, the, like the functions, like everything opened when you tapped it. There was no like glitch, there was no, the camera, everything worked

Similarly, another participant stated about the design when asked:
I like the simple breakdown into the six different sections, I think that’s what makes it user-friendly. Umm, I mean, it’s easy to follow when you go into like the different coping strategies and whenever you try to highlight the hyperlinks are really easy to kind of delineate what you’re looking for.

Learning how to use mSMART: Easy and Difficult. Whereas 90% of the sample indicated that learning how to use mSMART was easy, 10% of the sample indicated that it was difficult. Typical comments about learning how to use mSMART included:

> I think the app is actually pretty, uhh, like user-friendly. It doesn’t, it doesn’t take a whole lot of learning.

Features of mSMART that should be added. Ninety percent of the sample commented on features of mSMART that they thought should be modified. The most commonly endorsed feature that should be added was a snooze option for medication reminders (40%). For example, when discussing modifying the alarm feature of mSMART, one participant suggested the following change:

> Almost like on your phone if you snoozed or something … If something happens, it will alert you again. … to physically turn it off almost

Likelihood of using mSMART. The majority of the sample, 90%, commented on how they thought mSMART would be most appropriate for individuals either just starting PrEP or those who have PrEP adherence problems. In particular, 60% of participants—all of whom reported taking PrEP for at least five months—commented on how it would have been helpful to use mSMART when they began taking PrEP. For example, one participant commented on how mSMART would have been helpful when starting on PrEP:

> I do think, like the first two months probably would’ve been the time this app would’ve been the most helpful. … Cause there were also times that I straight up, like I forgot if I had taken it or not; in that first month

Another participant spoke less about his own initial difficulties with PrEP adherence, but spoke more broadly about individuals initiating PrEP:

> … as more and more people learn about it and find out about it that information might be less, so that there might be more questions about understanding side effects, especially in the first month where you’re most likely to have side effects. So like, I think that [is] where it can be useful. So like figuring out how do I cope with these side effects? Are they going to go away? What’s the duration? … Umm I think, one thing I can imagine is like, you know, suppose that when you’re first starting your medication, you’re less likely to have a routine, so you’re more likely to miss a dose, and in some cases you might wonder, well like what, let’s say I usually take my dose at 8 in the morning and its 3 in the afternoon, and I just realized I didn’t take my pill, should I take my pill or not? That’s a question that I think people might have, and your doctor may or may not have given you guidance on what to do in that situation … So, that’s an area where I can imagine the role this app can fill.

Discussion
The large-scale implementation of PrEP is an ongoing challenge that requires diverse models of delivery addressing multiple facets of the PrEP continuum of care [54, 55]. The current study was a four-week pilot trial of mSMART as a mobile health PrEP adherence intervention that includes CM, medication reminders, PrEP education, individualized behavioral strategies to address adherence barriers, and medication adherence feedback. mSMART also assess adherence in real-time using a camera-based medication event-monitoring tool. CM guidelines for mSMART in this study involved a fixed-ratio schedule of reinforcement in which participants received feedback that they earned $2 every time they logged a dose (whether using the camera feature or manually) as long as it was within a two-hour window of the time they listed as their daily dosing. Adherence outcomes, treatment feasibility, and treatment acceptability were examined in 10 young MSM already prescribed PrEP in the community. Findings from this treatment development study are preliminary, but yield promising results and indications for treatment refinement for future efficacy trials.

PrEP adherence outcomes were measured both objectively and subjectively. For the former, PrEP composite adherence scores based on TFV/TFV-DP were examined. Despite that baseline scores indicated a high level of adherence prior to using mSMART (i.e., 90% of the sample was at or above a level of PrEP adherence considered efficacious) and therefore a ceiling effect would likely occur, 30% of the sample’s scores improved at follow-up. Also, no composite adherence scores worsened over the course of the study. Our use of biomarker as an adherence outcome is strength given that there is substantial within-subject variability in adherence based on the measurement method selected among individuals on PrEP [56]. Alternative methods, such as self-report [57] and electronic pill bottles [58] among young MSM have noted limitations. In terms of a future direction, since PrEP adherence scores were already high rate at baseline, future studies are needed that address if mSMART improves PrEP adherence among those with a poor medication adherence history and if this impact on adherence is clinically significant.

The subjective measure of adherence was an adapted medication questionnaire measuring perceived PrEP adherence barriers administered at baseline and follow-up. While 50% of the sample did not report any change in barriers to PrEP adherence, 30% reported a decrease in barriers and 10% reported an increase in barriers. Participants who reported a decrease in barriers indicated that factors such as barriers associate with the financial cost of PrEP; the participant who reported an increase in barriers indicated that the belief that PrEP was helpful in reaching overall health goals had changed. Although these changes in perceived barriers (either increasing or decreasing) emerged, future studies that include a control condition are needed to address if these changes occurred because of mSMART or other factors. Overall, across methods of adherence examined in this study, findings were relatively consistent.

mSMART feasibility was positive as evidenced by 0% study attrition, the absence of any smartphone-compatibility events, and daily engagement with mSMART. Regarding the latter, we looked at rates of logged PrEP doses and the proportion that responded to all of the mSMART daily surveys. Using either the camera-based medication event-monitoring tool or manual entry option within a two-hour window of when participants identified the time they should take their PrEP pill, the overall adherence rate was 91%. Although CM guidelines in this trial considered a medication event valid either if there was a picture taken of the PrEP pill or it was entered
retrospectively, a more methodologically rigorous CM approach would require an objective assessment of behavior that does not rely on self-report (e.g., use of the camera-based medication event-monitoring tool only). Given that the majority of times medication adherence was reported via mSMART involved camera-based entries (88%), a more rigorous CM intervention appears feasible in future mSMART studies. In terms of responses to daily surveys on mSMART, 70% of the sample responded to all of the questions.

Feasibility was also examined by measuring the time it took participants to complete different tasks on mSMART. Although there is no standardization of scores on these tasks (i.e., the number of seconds to complete each task within mSMART), performance on these tasks can inform treatment development efforts, such as determining if basic procedures within the smartphone application are understood and can be executed independently [43]. In this sample, no prompts were requested by participants and the majority of tasks (92%) were carried out in 10 seconds or less, which indicated that mSMART was a feasible tool for young MSM on PrEP.

Acceptability of mSMART was examined with mixed results. Ratings on a four-point Likert scale indicated that participants on average “moderately” agreed that mSMART was usable on a daily basis and somewhat less than “moderately” agreed that overall they were satisfied with mSMART as an intervention to improve PrEP adherence, that they would be willing to recommend mSMART to others on PrEP, and that it was user-friendly. Difficulty learning how to use mSMART was minimal. The SUS indicated that 60% of the sample found the mSMART intervention usable. Although a sample size of 10 is small, guidelines for the SUS indicate that it measures perceived usability of a system with a small sample around this size [59, 60].

Qualitative analyses of exit interviews were conducted to complement these quantitative analyses of acceptability and examined aspects of mSMART that could be maintained, discarded, or adapted in future iterations. While some features of mSMART were generally perceived favorably (e.g., use of reminders, the camera feature, and daily questions), participants indicated that even these features could be adapted in future trials. For example, despite liking the medication reminder function, some participants expressed that a “snooze” function or multiple reminder alarms should be added. One particularly notable feedback theme was that mSMART was too text heavy with suggestions to minimize wording and make the display of such wording more visually appealing (e.g., in bulleted formatting, as opposed to lengthy paragraphs).

Although mSMART is a multi-component intervention (e.g., CM, behavioral skills training, use of reminders), one feature that we anticipated to emerge in our exploratory qualitative analysis was for participants to view CM favorably. However, other features of mSMART emerged that were favored more than CM. Therefore, as mSMART undergoes further development, comparative trials should consider its efficacy with and without CM. Similarly, it may be that reinforcer saliency (i.e., $2 for each logged dose) was too low for participants to find engaging and other CM approaches may be warranted. Although this could come in the form of a higher dollar amount as a reinforcer, the cost of such CM approaches may be prohibitive. To reconcile this, studies should consider lower cost CM approaches that are engaging (e.g., the “fishbowl” technique) [61-63] or a time-limited use of mSMART with higher reinforcer amounts (e.g., during PrEP initiation as was recommended in our qualitative analysis).
Future studies are needed to build on these pilot trial findings. In addition to the factors mentioned above, efficacy trials are needed to examine if mSMART improves PrEP adherence in comparison to a control group. This would necessitate larger samples that are statistically powered to detected group differences, as well as consideration of sample composition (e.g., those initiating PrEP or who have struggled with PrEP adherence at baseline, as opposed to the current sample in which 90% had protective levels at baseline and therefore may have already established adherence habits). Relatedly, although this study examined a group at-risk for HIV infection—young MSM—young Black MSM are a particularly at-risk group [17]. However, the sample for the current study was 70% White and did not contain any Black MSM, which limits generalizability. Finally, as PrEP use is extending into adolescent MSM, adherence interventions are needed that address unique challenges that emerge in working with this younger age group than those included in the current study [18].

In conclusion, this was a phase I trial of a mobile health intervention that aims to improve PrEP adherence. To our knowledge, mSMART, is the first PrEP adherence intervention administered via smartphones to integrate CM. Given its mobile health format and the ubiquity of smartphone use among younger populations recommended for PrEP [22], this is a PrEP adherence intervention that would be scalable and likely easily disseminated into clinical care settings. In clinical practice, mSMART could be integrated with electronic health records and allow for real-time communication between healthcare providers and patients. However, although our findings indicate that mSMART is a promising intervention to improve adherence rates, the results are preliminary and future studies are needed to demonstrate efficacy. These studies should also consider our findings indicating areas in which mSMART can be adapted to more comprehensively meet the needs of young MSM prescribed PrEP.
Acknowledgements

This work was supported by the Duke Department of Psychiatry and Behavioral Sciences Research Incentive and Development Program. This publication also resulted in part from research supported by the Duke University Center for AIDS Research (CFAR), an NIH funded program (5P30 AI064518). In addition, this publication resulted in part from research supported by the University of North Carolina at Chapel Hill Center for AIDS Research (CFAR), an NIH funded program (P30 AI50410). We thank Rebecca Pratt for assisting with data collection.

Conflicts of Interest

Dr. Mitchell has received royalties and/or consulting fees from New Harbinger Press, Intelligent Automation Incorporated, and Behavioral Innovations Group.
References


sex with men (YMSM) in self-reported versus biomarker data. AIDS Behav, 2017.
PMID: 29079950


Supplement A.

Participants were asked by an examiner to log into mSMART on their phone. From the main home screen, they were asked to complete the following tasks. They were asked to return to the home screen after completing each of the six tasks.

1. Show me where you go on the app to take a picture of your Truvada pill.
2. Change the time of your daily medication reminder.
3. Check to see how much money you’ve earned using mSMART.
4. Check to see if you have any questions on the SMART Desk.
5. Check to see if upset stomach is a side effect of using Truvada.
6. Related to the instruction above, what percentage of people who take Truvada experience an upset stomach at some point?

Supplement Table A. Exit interview task performance

<table>
<thead>
<tr>
<th>Exit Interview Task</th>
<th># of seconds M (SD)</th>
<th># of prompts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.93 (.81)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6.09 (2.69)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>5.77 (5.53)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3.90 (1.72)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>6.74 (4.33)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>6.88 (2.52)</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes. Overall mean across tasks was 5.39 (32.31/6)
Supplement B.

Supplement Table B. Qualitative theme endorsement rates

<table>
<thead>
<tr>
<th>Theme</th>
<th>Endorsement Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. mSMART features</td>
<td></td>
</tr>
<tr>
<td>Liked</td>
<td>20%</td>
</tr>
<tr>
<td>Disliked</td>
<td>0%</td>
</tr>
<tr>
<td>Mixed (liked and disliked features)</td>
<td>80%</td>
</tr>
<tr>
<td>2. Daily use</td>
<td></td>
</tr>
<tr>
<td>Facilitator</td>
<td>40%</td>
</tr>
<tr>
<td>Barrier</td>
<td>0%</td>
</tr>
<tr>
<td>Mixed (facilitators and barriers)</td>
<td>60%</td>
</tr>
<tr>
<td>3. mSMART aesthetics</td>
<td></td>
</tr>
<tr>
<td>Liked</td>
<td>10%</td>
</tr>
<tr>
<td>Disliked</td>
<td>40%</td>
</tr>
<tr>
<td>Mixed (liked and disliked aesthetics)</td>
<td>40%</td>
</tr>
<tr>
<td>4. Learning how to use mSMART</td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>80%</td>
</tr>
<tr>
<td>Difficult</td>
<td>0%</td>
</tr>
<tr>
<td>Mixed (easy and difficult)</td>
<td>10%</td>
</tr>
<tr>
<td>5. Features of mSMART that should be modified</td>
<td>90%</td>
</tr>
<tr>
<td>6. Likelihood of using mSMART depends on how soon you start PrEP or if you have adherence problems</td>
<td>90%</td>
</tr>
</tbody>
</table>

Notes. Themes 4, 5, and 6 were not commented on by one participant (therefore the sum endorsement rate is 90% instead of 100%).