Final Progress Report: The Wise App Trial for Improving Health Outcomes in PLWH

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Structured Abstract

Purpose: Given the dearth of useful and likeable apps, the need for improving medication adherence in PLWH, and the great promise of mHealth, we designed and tested a user-centered smartphone app linked to a smart pill box targeting antiretroviral therapy (ART) adherence in persons living with HIV (PLWH).

Scope: HIV continues to affect 1.2 million Americans. Achieving viral suppression through adherence to ART is a critical determinant of successful transmission prevention and long-term outcomes in HIV-infected patients. mHealth is a tool that has proven useful in supporting behavior change, but most mHealth tools for PLWH have not been well-developed or evaluated.

Methods: The aims of our study were to: (1) Build a functional app for HIV self- management linked to a smart pill box (Wise App) for PLWH and assess its usability; (2) Evaluate the impact of the Wise App on medication adherence in PLWH; and (3) Assess PLWH perceptions of the predisposing, enabling, and reinforcing factors for Wise App use through theoretically-guided focus group sessions.

Results: We found a significant improvement in ART adherence in the intervention arm compared to the attention control arm from day 1 (69.7% vs 48.3%, OR = 2.5, 95% CI 1.4-3.5, P = .002) to day 59 (51.2% vs 37.2%, OR = 1.77, 95% CI 1.0-1.6, P = .05) of the study period. From day 60 to 120, the intervention arm had higher adherence rates, but the difference was not significant.

Key Words: antiretroviral therapy (ART), HIV, mHealth, user-centered design, clinical trial

PURPOSE

Aim 1

The purpose of this study was to evaluate the usability of the WiseApp.

Aim 2

The purpose of this study was to determine the efficacy of WiseApp, a user-centered design mHealth intervention to improve ART adherence and viral suppression in PLWH.

Aim 3

The purpose of this work was to conduct an in-depth analysis to understand patients' experiences using a real-time medication monitoring pill bottle linked to an HIV self-management app.

SCOPE

Aim 1

Background

The Importance of Medication Adherence in HIV

Although HIV is now considered a chronic condition, sustained adherence to antiretroviral therapy is essential to disease management and maintaining viral suppression. Despite the development of simplified, single-tablet regimens, adherence remains difficult for some persons living with HIV (PLWH). Specifically, underserved populations, namely those with lower socioeconomic status and educational level, concomitant drug or alcohol use, and more complex medication regimens have an increased risk of nonadherence to HIV medications. Importantly, individuals with these same characteristics are disproportionately affected by HIV; therefore, it is a significant problem that requires effective interventions. There is evidence to support the use of mobile health (mHealth) application (app) for persons living with chronic illnesses to self-manage their health. HIV is now largely considered a chronic illness in the US and so the use of mHealth technology may have wide reaching implications across chronic illness populations (e.g. diabetes, cardiovascular disease). A recent study testing a symptom self-management mHealth app demonstrated that the intervention group receiving self-care strategies had a significant improvement in symptom burden and medication adherence compared with those in the control group ($p=0.017$). However, medication adherence was a secondary measure in the study and was limited to a self-report measure.

There is a paucity of self-management apps for PLWH. The following functional components were identified by PLWH as being components of an ideal mHealth app to support symptom and health self-management: communication, reminders, medication logs, lab reports, pharmacy information, nutrition and fitness, resources, settings, and search. A systematic search for commercially-available apps for self-management of health for PLWH, however, identified 15 apps, none of which had all of these functionalities. Specifically, none of these apps mentioned capabilities to link to external devices, such as an electronic pill bottle, or provision of nutrition and fitness information.

Given these data, our research team used participatory research methods to design a self-management app that contains real-time medication monitoring for PLWH in addition to the functional components previously identified. We developed a mHealth app ("WiseApp") for HIV self-management to help PLWH self-manage their health and monitor their medication adherence. The development of the app was guided by Fogg's functional triad for computing technology model which discusses modes for technology to affect behavior change. Important components to include in the app framed within this model include medication reminders (tools), testimonial videos (social actors) and to-do lists (medium). In addition, real-time medication

monitoring is important for medication reminder systems and it is both feasible and acceptable to PLWH.

Study Context

Significance of Usability Testing of mHealth Applications

Usability is the extent to which a user can use the IT system (e.g. website, computerized provider order entry system, mobile app) to achieve their goals, and how satisfied they are with the process. IT systems which do not adequately consider the needs of the intended end-users are often difficult to learn, misused or underutilized. mHealth technology has encountered similar challenges. As many of the inpatient IT systems such as Computerized Provider Order Entry (CPOE) and Electronic Health Records (EHRs) which were developed for clinicians with insufficient attention paid to the intended end-users and as a result some of these systems were related to fatal errors. Therefore usability has been widely recognized as a critical component in the development of health IT systems. More specifically, mHealth apps require a thorough understanding of the context of its proposed use by incorporating input from end-users to understand and improve the deficiencies of the technology and reduce the risk of failure. Even if a mHealth app is aesthetically appealing, if it is too difficult to use, users will become frustrated and unwilling to use the app. Therefore usability of mHealth apps becomes of critical import.

WiseApp

The WiseApp is derived from formative work to design a self-management app for PLWH, with the goal of being more widely applicable across chronic illness populations who require medications and additional self-management strategies. A comprehensive process for the design of the self-management is described elsewhere but in short, the work was guided by the Information Systems Research (ISR) framework and incorporated end-user feedback throughout the design process. The resultant WiseApp is comprised of the following functional components: 1) testimonial videos of PLWH, 2) push-notification reminders, 3) medication trackers, 4) health surveys, and 5) a “To-Do” list outlining their tasks for the day, such as medications to take and goal steps to take. A key component of the app is a medication tracker linked to an electronic pill bottle and a capability to link to a fitness tracker and monitor physical activity. The app can then send tailored reminders based on the feedback from the linked devices, such as medication reminders if the pill bottle has not been opened, or reminders to walk more steps. In addition to the home screen, the WiseApp has 3 additional domains including a screen to review medication adherence; a chat room; and a “Me” screen where users can set up their preferences and settings.

Aim 2

Background

Despite efforts to achieve UNAIDS 95–95–95 targets, deficits remain in HIV viral suppression and antiretroviral therapy (ART) adherence among some groups of persons living with HIV (PLWH). Progression of HIV disease and premature deaths among PLWH has been attributed foremost to poor adherence to HIV treatment regimens. Timely access to ART and subsequently sustained ART adherence is central to therapeutic success and is a critical determinant of long-term health outcomes (eg, viral suppression) in PLWH. For many chronic diseases, such as diabetes or hypertension, drug regimens remain effective even after treatment is resumed following a period of interruption. In the case of HIV, however, loss of virologic control because of ART nonadherence may lead to the emergence of drug resistance and loss of future treatment options. Effective interventions for PLWH with poor ART adherence is essential to improve health outcomes and continue making progress toward HIV target goals.

The abundant use of mobile health (mHealth) technologies creates opportunities for health behavior management tools that were not previously possible and has the potential to be used to support the healthcare needs of PLWH. The use of mHealth can reduce geographic and economic disparities and personalize healthcare, which is particularly relevant to PLWH since many are from underserved and minority groups.

mHealth technology is especially relevant in the context of improving ART adherence in PLWH. mHealth is focused on the use of mobile information and communication technologies to support care delivery through meeting information, communication, and documentation needs of clinicians, patients, and other healthcare workers and facilitating health resource monitoring and management. mHealth can provide mechanisms for improving the efficiency and effectiveness of care provided while reducing administrative burden.

Study Context

To that end, we developed an mHealth intervention, the WiseApp, using rigorous user-centered design research with underserved PLWH that draws on considerable formative work with PLWH, HIV clinicians, HIV case managers, and the Centers for Disease Control and Prevention (CDC) (U01PS003715, Principal Investigator [PI]: Schnall). We then built the mHealth application (app) and integrated it with a smart pill box (CleverCap) to allow PLWH to self-manage their HIV and monitor their medication adherence in real time. The WiseApp is derived from formative work funded by and in collaboration with the CDC (U01PS003715) to design a self-management app for PLWH with the goal of being more widely applicable across populations with chronic illness populations who require medications and adding self-management strategies. A comprehensive process for the design of the self-management app was guided by the Information Systems Research framework and incorporated end-user feedback throughout the design process. The resultant WiseApp is comprised of the following functional components: (1) testimonial videos of PLWH, (2) push-notification reminders, (3) medication trackers, (4) health surveys, and (5) a “To-Do” list outlining their tasks for the day, such as medications to take. A key component of the WiseApp is a medication tracker linked to an electronic pill bottle (ie, smart pill box). The WiseApp sends tailored reminders based on the feedback from the linked device (ie, CleverCap), such as medication reminders if the pill bottle has not been opened. The WiseApp is unique because in most cases mHealth technology has been developed without incorporating patient-centered outcomes research. There are currently hundreds of applications (apps) for PLWH, yet they have not been conceptualized using evidence-based research and/or a patient-centered design. Consequently, research is needed to improve the understanding of how mHealth tools can be appropriately designed, functionally operated, and effectively used by PLWH to enable the dissemination of evidence-based information.

Aim 3

Background

Use of mobile technology in healthcare has expanded. Mobile health (mHealth) technology offers the opportunity to empower patients to engage in their own healthcare, by allowing patients to self-manage their health conditions. Further, mobile self-management apps have successfully improved health outcomes such as medication adherence, engagement in healthy behaviors and health-related quality of life. Recent evidence supporting feasibility and acceptability of mHealth interventions for improving medication adherence and self-management in chronic diseases is growing. Building on this evidence and specific to persons living with HIV (PLWH), a symptom self-management app was found to be efficacious in

improving symptom frequency and intensity and medication adherence in persons who used the app as compared with those in the control group (p=0.017). However, in these studies, medication adherence was limited to a self-report measure as a secondary outcome, which has limitations including reporting bias and over-estimating adherences.

Strict adherence to antiretroviral therapy (ART) among PLWH is essential to sustain viral suppression, prevent progression to AIDS and opportunistic infections, improve overall health and reduce the risk of sexually transmitting HIV to partners. Despite the known importance of taking HIV medication as prescribed, PLWH's non-adherence remains a critical problem. Several reasons such as HIV stigma, questioning efficacy/dosing of ART, and interactive toxicity beliefs regarding alcohol/drugs are associated with poor adherence. Additionally, existing literature shows that the most commonly selected barriers to ART among PLWH were being 'away from home', 'simply forgot', 'change in daily routine', and 'fell asleep through dosing time'. Approximately half of PLWH in the US are virally suppressed, indicative of the importance of improving long-term medication adherence using effective interventions to address existing barriers and enhance the HIV care continuum. For example, mobile interventions utilizing mHealth technology have been effectively used to monitor adherence to anti-depressants and schizophrenia and provide real-time adherence counseling in PLWH.

For the success of the long-term HIV care interventions utilizing mHealth technology, it is essential to support the quality of technology in PLWH's use because use of technology and user adoption is closely related to the usability of the system. Usability is the measure of the quality of a user's experience and is assessed through the interaction of user, system and task in a specified setting. Technology produced with poor design and inadequate consideration of the needs of their intended users will likely be misused or underutilized. Thus, it is necessary to ensure that technology works properly to achieve users' goals. This can best be achieved through an in-depth understanding of users' experiences in their everyday lives relevant to the use of mHealth technology, by including intended users' input in the design process, and identifying needs of the targeted users and taking into consideration of specific aspects of the technology throughout the development process.

Study Context

Using an iterative design process, our study team developed the 'Wise App', an HIV self-management app with real-time medication monitoring. The Wise App is comprised of testimonial videos of PLWH, push-notification reminders for medication adherence and physical activity, a medication tracker, health surveys and to-do lists outlining wellness tasks for the day (i.e., taking medication and walking steps). Specifically, the app is tailored to help PLWH self-manage their health and is linked to an electronic pill bottle to monitor medication adherence and a fitness tracker to monitor physical activity. This study focused on the electronic pill bottle, one of the two connected devices with the Wise App.

The Wise App is linked to an electronic pill bottle, the CleverCap™ LITE (a diameter of 2" and a height of 1.35"). This pill bottle records when the pill bottle is opened for medication ingestion and transmits patient identifier and date-time stamp over existing cellular networks in real-time. The CleverCap™ LITE beeps every time it is opened. Once closed (closed at least in five seconds after being opened), it flashes and sends a signal to a cloud, connecting with a cellular device/app (Wise App).

METHODS

Aim 1

We conducted a three-step usability evaluation using 1) a traditional think-aloud protocol with end-users, 2) a heuristic evaluation with experts in informatics, and 3) a cognitive walkthrough with end-users.

Usability Testing

Sample

End-users: Our sample was comprised of targeted end-users and informatics experts. We recruited from clinics and community-based organizations in the Washington Heights neighborhood in northern New York City. Out of 24 potential participants screened, 4 were ineligible due to incompatible technology or not being comfortable using a smart phone. End-users were eligible if they were HIV-positive, over the age of 18 years, owned a smartphone (equal number of participants for both Android and iPhone), and could read and communicate in English. The rationale for 20 participants is based on past usability research, which has indicated that 95% of usability problems can be identified with 20 users. For the usability testing, we did not require adherence criteria for eligibility because we were not testing the effectiveness of the app. We also administered a modified version of the Mini Mental State Examination (MMSE) for cognitive screening, assessing their orientation (asking for the date/season and location by state or city), registration (naming 3 items and asking to repeat), attention and calculation (counting by serial 7's at least to 21, and spelling a word backwards), and recall (asking again for the 3 items at the end of the screen). End-users were eligible if they were able to answer all the responses correctly.

The mean age of end-user participants (n=20) was 51.3 years (range 27 – 68). 70% of end-users reported their race as African American/Black, and 45% reported their ethnicity as Hispanic/Latino; 45% of the end-users had completed some high school or less. 45% of end-users reported an annual income less than $20,000 although 25% reported they did not know their income, and 45% of end-users had not completed high school. Ten end-users owned an iPhone, and the other 10 and Android. End-users all reported that they use their smartphones at least daily and 18 out of 20 reported using it multiple times a day. In addition, all end-users had been using their smartphones for at least 2 years.

Experts: Experts were eligible if they were experts in the field of biomedical informatics, specifically human computer interaction (HCI) and usability testing. Experts were invited by email to participate by the study team.

The mean age of the heuristic evaluators (n=4) was 54.3 years (range 41 – 67) and all reported English as their primary language. All 4 experts had a PhD and had an average of 19.5 years of experience in the field of bioinformatics (range 15 – 30). One expert had experience researching HIV and 3 were nurses with extensive training in medication monitoring and promotion of health activities including physical activity monitoring. Thus, they were dually-qualified to contribute to this usability evaluation.

Procedures

End-users and experts were given a list of 26 tasks to complete related to the functionality of the app, including managing the medication profile, reviewing medication adherence history, and identifying their goal steps to take for the day. Completion of each of the 26 tasks while using the app was recorded using Morae software™ (TechSmith Corporation, Okemos, MI). This software allows for audio and on-screen movement recording simultaneously. In addition, the Morae software™ was recorded using a mirroring recording on the study laptop; this allowed the study team to both observe the movements of the participants in real-time from the laptop as well as record the session for later viewing and analysis. Research staff, consisting of two nurse scientists (postdoctoral trainees), one nurse practitioner

(predoctoral trainee), and one coordinator with a MPH degree, also took field notes during each interview, or session. Both experts and end-users were asked to go step-by-step through the 26 tasks and to evaluate the app using a think-aloud protocol. Research staff prompted participants to describe their thought process when attempting to complete a task but were encouraged not to provide any specific guidance to participants. Occasionally, the research staff provided prompts when the participants were unable to complete a task; we recorded all instances of help to study participants. The interviews were analyzed using the interview recordings and were not transcribed.

In addition, following the usability testing, both end-users and experts completed a survey to collect demographic information as well as the Health-ITUES instrument to evaluate usability. Surveys were completed through Qualtrics and all data was stored for later analysis. In this survey, participants rated the app's usability using Health Information Technology Usability Evaluation Scale (Health-ITUES; scored 0–5; a higher score indicates higher perceived usability).

Data Analysis

All interviews were analyzed by the study team using the audio and video recordings of the app use. Each task was coded dichotomously (i.e., 1=easy, 2=not easy) and the proportion of participants who were able to complete the task easily were calculated. Any task that required assistance from the research staff was coded as "not easy". Of the 24 total interviews conducted for the think-aloud and heuristic testing (end-users n=20; heuristic experts n=4), 60% of the interviews were double-coded by two members of the research team, and any disagreements were resolved through discussion and reviewing the Morae video recording if necessary. In addition, qualitative comments were extracted from the interviews during the coding procedures if they were related to the perceived usefulness.

Cognitive Walkthrough

Building on our findings from the traditional think-aloud protocol with end-users and the heuristic evaluation with experts, we then refined the task list and conducted a cognitive walkthrough (CW) to provide more depth and granularity to our evaluation approach.

Sample

We recruited 10 PLWH who had not participated in the first part of this study. Because 20 PLWH participated in the think aloud protocol and we were testing the same app, we chose 10 participants as this number of participants would be sufficient to identify at least 80% of usability problems. We screened 16 potential participants, of whom 6 were ineligible due to incompatible technology (not having a smart phone) or not comfortable using a smart phone.

All of the end-users owned a smart phone; 5 reported using an iPhone and 5 an Android phone. The average age of the participants was 54.5 years (range 39–63), 70% reported African American/Black as their race and 40% reported their ethnicity as Hispanic. Fifty percent reported an annual income of less than $20,000, although one end-user reported not knowing, and 30% of participants had not completed high school. All participants could read and communicate in English and met the same criteria as required in the initial usability testing on the modified MMSE previously described. All participants reported using their smartphones at least daily and 8 out of 10 participants had been using their smartphone for at least 2 years.

Procedures

The CW evaluates the ease with which users can perform a task with little formal instruction or informal coaching. Compared to other usability testing methods, the CW is more structured with a goal of understanding a technology's learnability, and it can be especially useful when developing technology intended for individuals with low health literacy. The CW

session is comprised of: 1) a detailed design of the user interface 2) a task scenario 3) explicit assumptions about end-users 4) the context of use and 5) a sequence of actions that would allow the user to successfully complete the task. Participants in the CW are then asked to complete a set of tasks and describe their thought process while doing so. During task completion, the evaluator assesses the potential end-user's ability to identify, achieve, and interpret the correct action that is required for each step in the task. If all tasks are completed in the sequence of actions described in step 5 of the CW, then it can be determined that there are not any usability concerns at this stage.

The CW focused on the major tasks that were identified during the initial think-aloud and heuristic usability testing as either challenging or integral to the app functionality, specifically: 1) medication management, 2) routine set-up that informs the medication reminder system and 3) navigating to the different sections of the app. In addition, during this phase of the study, we tested the end-users ability to use external devices that connected with the app, specifically, an electronic pill bottle and a fitness tracker with the study app. Both devices can be linked to the app to provide reminders about taking medications and meeting the daily step goal. A predetermined list was developed in an iterative process by the study team after coding and analyzing the initial usability testing. The list consisted of high-level tasks, end goals that required multiple tasks, or sub-tasks to complete. End-users were asked to complete 10 high-level tasks which translated into 31 sub-tasks.

At the start of the study visit, participants were given basic information about the capabilities of the app as well as the list of high-level tasks. They were then asked to complete each task and think-aloud as they were attempting to complete each task. The research staff informed the participants that they would not provide guidance unless the task was found to be impossible to complete without assistance at which point they would ask open-ended questions to help guide the participant. Similar to the initial analysis, end-users rated the app's usability using Health-ITUES. All activities were recorded using Morae software and interview notes were taken during each interview by the research staff.

Data Analysis

The analysis was completed using the Morae recordings, field notes, and Health-ITUES scores. Each sub-task was analyzed and coded for 1) the number of actions it took for the participant to achieve the task and 2) if any assistance was provided to the participant by the research staff. The mean number of actions for each sub-task was calculated in addition to the mean number of users who required assistance. Of the 10 interviews conducted for the cognitive walkthrough testing (end-users n=10), 20% of the interviews were double-coded for inter-rater reliability and any disagreements were resolved by discussion among the team member and re-review of the Morae video recordings. The mean of the overall Health-ITUES score for the WiseApp was also calculated.

Aim 2

Study design and participants

This study was a randomized controlled trial (RCT) of the WiseApp intervention group versus an attention control group on ART adherence in PLWH which was measured daily through the CleverCap. Recruitment was completed in New York City at HIV and dental clinics, and community-based organizations (NCT03205982). Online advertising through Craigslist and other social media tools were also used to recruit study participants. Study enrollment was from

January 31, 2018 to April 13, 2021, and included a complete pause on enrollment due to COVID-19 from March to July 2020.

Eligibility criteria included: (1) 18 years of age or older, (2) have a diagnosis of HIV, (3) speak and understand English or Spanish, (4) live in New York City, (5) own a smartphone, (6) currently taking ART medications, and (7) report the past 30 days adherence of 80% or less as measured using the Visual Analogue Scale or have a viral load of over 400 copies/mL.

Columbia University served as the institutional review board for all study activities (the full trial protocol is available open access elsewhere).[15] Written informed consent was obtained for each participant. Participants were incentivized for study visits ($40 for the initial visit, $50 at 3 months with up to $25 additional for completing app challenges, $60 at 6 months with up to $25 additional for completing health-related activities such as quizzes and activities within the app) and received the WiseApp, a FitBit, and CleverCap pill bottle at the initial visit. Both study arms also have a history tab to monitor whether or not they completed their assigned daily goals. Both study arms also received the CleverCap pill bottle, with only the intervention group linking the pill bottle to the WiseApp.

Intervention

The WiseApp comprised the following functional components: testimonials of lived experiences, push-notification reminders, medication trackers, health surveys, chat rooms, and a “To-Do” list outlining tasks for the day. Testimonials of lived experiences were drawn from publicly available videos comprised of content related to patients’ experiences disclosing their HIV status, communicating with providers about health problems, and overcoming ART adherence challenges. Both study arms received a fitness tracker (ie, FitBit) that connects to the WiseApp. The WiseApp intervention originated from formative work to design a self-management app for PLWH. The intervention group received videos and health surveys all centered on medication adherence and managing living with HIV and the intervention group also received daily app notification reminders for taking their medication.

Attention control

The attention control group was given access to a mHealth app developed by our study team which was comprised of health promotion videos and surveys focused on a healthy lifestyle including exercise, diet, and sleep. Participants were also given a step goal and reminders to reach 5000 steps per day to improve their cardiovascular health.

Randomization

Study participants were randomized (1:1) to the WiseApp intervention or the attention control arm with a variable-permuted randomized block design with the block size randomly selected between blocks. The treatment assignments in the block design were predetermined by the study statistician before beginning the RCT and remained static throughout the trial. Random assignments were concealed from the participants for the duration of their participation while study staff members were aware of the participant’s randomization. At the baseline visit, study staff opened a sealed study envelope and created the profile in the app that aligned with the study group.

Study assessments

Participants completed standardized quantitative assessments of demographic characteristics (ie, age, race/ethnicity, and employment status) and health literacy[17] at baseline

via Qualtrics. The primary outcome for this study was a change in ART adherence measured daily through the CleverCap™ dispenser. The CleverCap automatically records each time a participant opens the dispenser. We collected adherence data each day from the start to the end of the trial (day 1–6 months), and it is a count response (number of times taking medication each day).

A number of secondary outcome measures were collected at baseline, 3 months, and 6 months. Blood draws were obtained through venipuncture at each study visit to measure CD4 counts and viral load. Self-reported adherence to ART was measured through the Center for Adherence Support Evaluation (CASE) Index. The CASE Adherence Index is a self-administered instrument with items scored such that higher values indicate better adherence, and the maximum total score is 16. Scores of 11 or higher on this index indicate good adherence (Cronbach's α = .79). Participants also completed the Healthcare Provider Engagement (HPE) Scale measuring their engagement with healthcare providers. Items are scored such that higher scores indicate a more negative relationship with their healthcare provider, where the maximum total score is 52. Participants also indicated their last primary care visit within the past year.

Statistical analysis

We enrolled 200 PLWH who reported suboptimal adherence to their ART regimen. We estimated that this would have greater than 80% power to detect at least a 10% difference in adherence to ART medication between the WiseApp intervention and the control arm. We made the following assumptions in our sample size and power calculation: a 75% retention rate by the end of the trial for both the control and intervention arms and that each person would be on a once-daily regimen, a conservative assumption of high intraclass correlation coefficient of .5 for the same participant at different times, and the adherence rate would be less than or equal to 80% at baseline. All calculations were based on a 2-sided test with alpha at .05 levels and power calculations being based on ART adherence.

We utilized a generalized linear mixed model (GLMM) to exam the WiseApp intervention efficacy on our primary outcome and secondary outcomes. The primary outcome, ART adherence, was measured daily from day 1 to the end of the RCT (or the last day before dropped out). A logistic GLMM with an individual-level random intercept was used to estimate the percent of ART adherence at each day. In this model, the dependent variable was ART adherence (coded as Yes/No) at each day, and the main dependent variables were (1) intervention arms; (2) days (from day 1 to end of the study); and (3) interaction term between arm and day. Since this is an RCT design, we reported unadjusted results (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf). The main analysis of all participants was followed by a sub-analysis by limiting to participants with a detectable viral load at baseline.
Secondary outcomes, including CD4 count, viral load, primary care visits, HPE, and CASE adherence and App Use, were measured at baseline, 3 months, and 6 months. GLMMs were used with appropriate link functions based on types of outcomes: identity link for continuous outcomes, logit link for binary outcomes, and log link for count outcomes. In this model, outcomes were modeled at the 3 time points (baseline, 3, and 6 months). We calculated interaction terms between study arm (ie, intervention vs control) and each indicator for time following the baseline observation, indicating a difference in the rate of change from baseline to each timepoint across the 2 arms. GLMM estimates for longitudinal data were unbiased under the missing at random assumption. Analyses were conducted in SAS 9.4

Aim 3

Sampling and Recruitment

Following the iterative development of the Wise App, we began a randomized controlled trial in January 2018. Our study seeks to enroll 200 PLWH into a 6-month trial (100 randomly assigned to the intervention group, 100 to the control group). Inclusion criteria are: HIV-positive, over the age of 18, ownership of a smartphone, able to speak and understand English and self-report less than 80% adherence to ART medications in the past 30 days or a viral load of over 20 copies/mL (detectable). Using flyers and posting on social media, participants were recruited from clinics at Columbia University Medical Center/ New York-Presbyterian Hospital and community-based organizations across New York City.

At the baseline visit, study participants were provided with two devices, an electronic pill bottle and a fitness tracker, linked to the Wise App. Participants in the intervention group receive push-notification 'medication' reminders based on the use of the electronic pill bottle. At the 3-month follow-up visit, intervention group participants were invited to participate in a one-on-one in-depth interview to share their experiences using the electronic pill bottle linked to the Wise App.

Procedure

Each participant was explained the study and signed an inform consent form prior to participation. Using a semi-structured interview guide, participants were encouraged to describe their experiences with the electronic pill bottle linked to the Wise App in their everyday settings. All interviews were audio-recorded with two digital recorders to safeguard against mechanical failure.

Data Analysis

Descriptive statistics using SPSS version 24.0 (IBM Corp, 2015) were used to analyze demographic information. Research team members (HC, GF and MS) independently reviewed the transcripts of the audio recordings, two research team member (GF and MS) independently generated a set of codes from the line by line codes via inductive content analysis and a third (HC) reconciled coding discordance between the other two GF and MS. Thematic analysis was used to identify themes with similar patterns across interview data. Discrepancies in the themes were discussed until consensus was achieved. A codebook was developed using Excel. Free text excerpted from the transcripts was entered into the codebook followed by each of the themes.

The Fit between Individuals, Task and Technology (FITT) framework was used to guide the coding of the interview data. Each of the themes in the codebook was categorized into the constructs of the FITT framework: fit between individual and task, fit between individual and technology, and fit between task and technology. The FITT framework postulates that adoption of health information technology (IT) depends on the fit between the attributes of the individual users (e.g., motivation), attributes of the technology (e.g., usability, functionality, performance), and attributes of the tasks and processes (e.g., task complexity). In the FITT framework, an 'individual' signifies an individual user; 'technology' represents for the interaction of tools needed to accomplish a given tasks; 'task' comprises tasks and working processes that should be completed by the individual user and that are supported by the given technology. The FITT framework facilitates an in-depth analysis of a variety of interconnected factors further influencing the success or failure of technology adoption.

Results

Aim 1

Usability Testing

The ease of executing a task for both end-users and experts for the 26 tasks. 19 of the 26 tasks were easy to complete for at least 50% of the end-users. Entering the section "My

Medication" was the task that was the least easy to complete. Although only 12.5% completed the task "complete a mission" easily, many participants did not attempt to complete this task. In addition, both the experts and end-users reported the following tasks as difficult: 1) adding new medications and 2) reporting medications as taken. The mean of the overall Health-ITUES score for the WiseApp was 4.39 (SD=0.55) for end-users and 3.63 (SD=0.80) for experts suggesting that the end-users perceived the app to be usable.

These results were summarized and discussed with the developers of the app, and updates were made to reduce the difficulty in using these components of the app. For example, the color of the dock domains was made darker and the text on the home screen was darkened to improve visibility. In addition, the "Missions" were felt to be irrelevant or redundant to the "tasks" for the participants, and this functionality of the app was removed. Finally, the "Me" screen was renamed to "More" for clarification.

Cognitive Walkthrough

19 of the 31 tasks were easy to complete, requiring less than 2 steps on average. The tasks that took more steps to complete on average were frequently related to finding a specific section within the app. For example, the "To-Do" list was frequently cited as being difficult to find on the home screen (mean=8.3, range 3–22 steps): *"for me, it would be easier if it was under my meds that I'd entered…maybe it could be in bolder, bigger and bolder, say if you wear reading glasses"* (end-user 31). Confirming that a medication, which can be noted on the home screen, also took more steps on average, suggesting that this section should be made more visible: ""what do I go to…open it again?...press more? It should be bolder, easier to see" (end-user 27). This informed additional iterative updates to the app as well as the development of an onboarding procedure for future end-users participating in the ongoing randomized controlled trial (https://clinicaltrials.gov/ct2/show/NCT03205982). The mean of the overall Health-ITUES score for the WiseApp was 4.21 (SD=0.70), similar to the end-users in the usability testing phase, further suggesting that the end-users perceived the app to be usable.

End-users had more difficulty confirming the number of steps they had taken with the fitness tracker compared with other tasks; however, some participants were positive toward this capability once they saw how to link and track their steps: ""I love it because it's like one of these that's going to remind me that I have to take my medication!" (end-user 33). Other participants, however, found the connection of a device to the app confusing: "I think that was the most confusing one out of all of them…the pill box was great, but to get to this… (connected device)…see I wouldn't even know what to do with that. After I connect to the device, what do I do? I think it would be easier if it explained to me what it was doing...more details. I don't really care how many steps I take" (end-user 32). Therefore, some end-users may need further information about the purpose and capabilities of using a fitness tracker.

This multi-component usability evaluation, the ease of completion for the think aloud protocol and the more granular task analysis provides a complete picture of the usability of the app for the end-user population PLWH. The end-users in both groups perceived the app to be usable as measured by the Health-ITUES scores (4.39 and 4.21 respectively).

The medication tracking bottle was easy to navigate requiring 1.7 steps on average to complete the task of opening and closing the bottle, and many end-users reported that it could be helpful: "this is pretty easy because it says push…that right there was very very complicated" (end-user 25). However, others had some concerns about the tracking device: "I don't need some pill bottle with the flashing lights…it's basically programmed in my head, I just do it" (end-user 27). End-users sometimes required some guidance confirming that the medication was taken showed up on the home screen (mean steps to complete task: 5.75; range: 1–18): "oh I got it! sorry" didn't see the "past" banner".

Aim 2

Sample characteristics

From July 2017 to April 2021, 1175 individuals were screened, 200 were enrolled, and 200 were randomly assigned to 2 arms: 99 individuals to the WiseApp intervention and 101 to the attention control arm.

In terms of race, 146 (74%) of participants were identified as Black/African American, 29 (15%) as unknown/missing, 13 (7%) as White, 1 (0.5%) as American Indian/Alaskan Native, and 2 (1%) as Native Hawaiian/other Pacific Islander. By ethnicity, 51 (26%) participants were identified as Hispanic/Latino (any race). Mean (SD) age was 49.3 (10.5) years. A total of 11 (6%) of participants were working full-time, 26 (13%) of participants were working part-time, and 102 (52%) of participants were unemployed or retired.

Primary outcome

The full sample for analysis of intervention efficacy was $n = 198$. Participants randomized to the WiseApp arm had significantly higher daily ART adherence rates compared to those randomized to the control arm from day 1 (69.7% vs 48.3%, OR = 2.5, 95% CI = 1.4–3.5, $P = .002$) to day 59 (51.2% vs 37.2%, OR = 1.77, 95% CI 1.0–1.6, $P = .05$) of the study period. Adherence rates then began to decline over the study period for both arms ($P < .0001$ for both arms) and the rate of decline was faster for the intervention arm as compared to the control arm ($P < .0001$). At day 60, there was no significant difference in ART adherence between the 2 study arms, but the intervention arm had adherence rates than the control arm participants.

The sample of cases with detectable baseline viral load for subanalysis was $n = 119$. In this subsample, participants randomized to the WiseApp arm had a nonsignificant higher ART adherence compared to those randomized to the control arm right at the start of the intervention (50.6% vs 44.2%, OR = 1.3, $P = .48$). For both arms, adherence declined over time throughout the entire study period ($P < .0001$ for both arms). The decline was significantly faster for the intervention arm than that for the control arm ($P < .0001$), and by around 2 months, there was no difference in ART adherence between the 2 arms.

Secondary outcomes

In all study participants, even those who were detectable at baseline, there was not a significant difference in detectable viral load change between the 2 arms (P = .89). For each arm, there was not a significant decrease in detectable viral load from baseline (P = .09–.49). For those randomized to the intervention arm, CD4 count did not significantly change from baseline to 3 months (P = .81) and 6 months (P = .11). For those randomized to the control arm, CD4 count declined significantly from baseline to 3 months (declined 16.2%, P = .04) and 6 months (declined 25.4%, P = .01). However, the difference change between the 2 arms was not statistically significant (P = .25). For those randomized to the intervention arm, CASE adherence index increased significantly from baseline to 3 months (increased 0.38 points, P = .0002) and 6 months (increased 0.39 points, P = .0002). For those randomized to the control arm, CASE adherence index increased significantly from baseline to 3 months (increased 0.38 points, P = .0001) and 6 months (increased 0.39 points, P = .0002). There was no significant difference in change in CASE adherence between the 2 arms (P = .99).

There was no observed difference in self-reported attendance at primary care visits between the 2 arms (P = .51). There was also no significant difference in healthcare provider engagement between the 2 study arms (P = .19). Retention rates for each of our study arms remained at or above 75% throughout the study. Our retention rates were based on both

attendance at the study visits and on reports of daily adherence. At 3 months, we retained 84% of study participants in the intervention arm and 89% in the delayed intervention arm. At 6 months, we retained 80% of study participants in the intervention arm and 85% in the delayed intervention arm.

App Use was measured as the mean number of days that each participant used the app. At 3 months, intervention group participants used the app a mean of 57.8 days as compared to the control group which used the app a mean of 46.4 days with a statistically significant difference between the groups ($P < .05$). At 6 months, mean app use decreased in both groups to 42.0 days in the intervention group and 40.5 days in the control group with no significant difference between groups ($P = .77$).

Aim 3

Sample

Thirty-eight PLWH participated in the in-depth interviews. The mean age for study participants was 47.6 years (*SD*=10.9; range 26–68 years of age). The majority (n=30; 79.0%) of participants reported their race as African American/Black, and 15.8% (n=6) of participants self-identified as Hispanic/Latino. 60.5% (n=23) of participants were female, and half the participants (n=19; 50.0%) were single. 63.2% (n=24) of participants had completed some high school or less. 79.0% (n=30) of participants reported an annual median income of less than $20,000, although 15.8% (n=6) of participants reported that they did not know their annual incomes.

Fit Between Individuals and Task

The three themes related to fit between individuals and task were: 1) motivation for strict medication adherence; 2) self-efficacy for overall health management; and 3) engagement with medication reminders.

Motivation for strict medication adherence

Participants understood the importance of adhering to their medication regimens but still found it challenging. Participants expressed that using the electronic pill bottle motivated them to take medication, and they were better able to track their medication adherence as well. Several participants stated, *(P027) "My experience with the pill bottle is that it keeps me motivated. It also helps me know basically when it's time to take my medication." (P005) "It gives me more encouragement to take my medication on time every day." (P070) "It has been very useful with me taking my medication. Whereas on average I probably would miss taking my meds maybe eight or ten times out of a month, now I don't hardly miss. If anything, it's maybe three times a month. I know I should take my med. I am improving." (P041) "This has helped me keeping track of my time, and taking it [medication] every day at the same time. Hopefully, by the end of my study, I will do it automatically because I will be already adjusted to the time." (P081) "It keeps me on track of the medication I'm taking and trying to get my viral load and T-cells at a level where it's supposed to be."*

Self-efficacy for overall health management

Participants wanted to improve their general physical health. Participants expressed self-efficacy for health management by monitoring medication adherence through the electronic pill bottle linked to the Wise App. Participants mentioned, *(P004) "It helps you to keep track of your meds… then your general health... I guess that's why they called it Wise App… it's been real helpful. I feel I can take care of my health" (P029) "…like I say, the Wise App and pill bottle, which has kind of made me more active. Like to be more present in what I am doing in life…"*

(P081) "I would keep using it, to keep my health above water…I would recommend anybody to use it."

Engagement with medication reminders

Participants described how they often forgot to take their medication on time every day and the electronic pill bottle facilitated adherence to their medication schedule. Several participants highlighted the need for reminders to take medication exactly as prescribed. They explained, *(P039) "Like when I have a busy day and my memory is not too good, because I'm running around doing stuff and I'm living life like I'm supposed to, it reminds me on my phone by putting a message. And it comes up. And I look at my phone. And I notice; oh my god. I didn't take my medicine."(P055) "Like I would go four days without taking it. Or my memory is short now. And my memory is not as much as good as it was before. So I really need this to help remind me to take my medication."* Participants appreciated receiving push-notification medication reminders to encourage adherence to their daily medication schedule (i.e., whether they did or did not open the electronic pill bottle on time every day). Several participants mentioned, *(P004) "It gives me more time with my medication because I wasn't – I'd know to take it, but I didn't have a reminder, so this has been a real reminder to me, and it's helped me to stay on it…" (P055) "I mean I feel like now it's more efficient. It's a lot easier. And in terms of like it pops up, so it's in my conscience. And I won't dismiss it unless I take it. So even if I pass let's say the timeframe, I still know that I need to take it. So I'll still take it." (P089) "I think the reminder is very useful…When I read that, it's like; 'Oh, is it almost time?' That helps a lot because I just pick up my phone and it's just there."*

Fit Between Individuals and Technology

The four themes related to fit between individuals and technology were: 1) ease of use; 2) HIV-related stigma and disclosure of HIV status; 3) customized alert of medication time windows based on individual routine set-up; and 4) preference for device design.

Ease of use

Some participants reported that the electronic pill bottle was easier to open than their regular pill bottles. Several participants described, *(P002) "It's easy to open. So it's a little easier to open than some of my regular pill bottles. I've got to fumble with them to open them up."* Moreover, many participants thought the translucent bottle made it easy to check the number of pills left in the pill bottle. Another participant said, *(P029) "I can automatically know to pour it – I don't have to shake it to see how many is in there. I can see and it's easy to fill."*

HIV-related stigma and disclosure of HIV status

Participants explained how some of their concerns about HIV-related stigma and disclosure of HIV status were resolved through the use of the electronic pill bottle. They described the discreteness of the electronic pill bottle since it does not have any HIV medication labels (this facilitated privacy regarding their HIV status). Some participants elucidated, *(P004) "Now when you have the bottle from the pharmacy, it says Reyataz or Epzicom or whatever. That one [electronic pill bottle], that don't say what it is. It could be any pills, any medications. So it's not like an indicator that people know me HIV…" (P041) "It's more...discrete, discrete... It doesn't show what medication I am taking…because it doesn't say it on the bottle." (091) "I'm comfortable pulling this out and taking the pill, instead of pulling my medicine out...This thing's got nothing to do with HIV. So I'm clear on that."* In addition, one participant recounted how she was able to maintain privacy with the electronic pill bottle when around her family. She stated, *(P029) "I've been HIV for 20 years. I have a 19-year-old daughter. And I've never*

disclosed to her my HIV status. So she asked me one day about it. I told her, I said, it's for pain medicine. The pill box is not marked like that, you know. You can't read that it's an HIV-related pill bottle. I am happy to have it."

Customized alert of medication time windows based on individual routine set-up

Participants thought the customized medication alert was a useful feature, because they were able to tailor medication reminders around their meal/bed times on the app in connection with the electronic pill bottle. Several participants stated, *(P043) "I like it. It really helps, especially if you're having a busy day, you're running late, or you're running around." (P006) "It is a good fit with my life. I had 10 o'clock. That's what I'm aiming for. But, normally I stay up so late at night that I take it, like in the three hours of the morning. I'm trying to change that routine and trying to at least take my pills before midnight." (P044) "It's just that I was missing the timeframes, because of my schedule. So it was frustrating. But then once I changed the routine and I realized, okay the mornings are better… it's just easier for me. I just changed that around. And then it got a lot less stressful."*

Preference for device design

Several participants explained that the electronic pill bottle was too small to fit their whole medication regimens or was too large to conveniently carry with them. Additionally, some participants found the lights to be exceedingly flashy and found the beeping irritating, especially when trying to conceal that they were taking medication.

Participants described, *(P008) "I really like this pill bottle. However, the only thing I have against this pill bottle is that I take more of the pills. I need bigger one." (P009) "Well, first of all I left it home – I didn't have to travel with it because it was very difficult to travel with. Because you would have to carry something big enough to carry the bottle, because it's very delicate." (P051) "It lights up. And it's just, I don't know. I live with my girl. So it just notifies every time I'm taking it or not taking it. So it's just a conversation I don't want to have. So I just move it to the side." (P084) "…if I were to take it with me or something like that, it's a little too bulky for just a pocket. Certainly in the summer, this would be brutally inconvenient for me."*

Fit Between Task and Technology

The two themes related to fit between task and technology were: 1) system functionality of data transfer from the electronic pill bottle to the app; and 2) self-awareness of system syncing signals.

System functionality of data transfer from the electronic pill bottle to the app

Some participants experienced technical issues such as the data not syncing between the electronic pill bottle and the app as prescribed by the CleverCap™ LITE. For example, some participants received push-notification medication reminders even after they had taken their medication. A few participants reported their technical problems by stating, *(P006) "So I feel when it doesn't beep it's a problem. It just won't get it if it don't beep right… sometimes it doesn't register that I took it at that time." (P043) "Once in a while, even though I've taken it, it doesn't update my phone for a couple of hours. I would be thinking that I wasn't taking my meds? And then I thought I broke it, which I didn't. There was something wrong with it." (P033) "There was a few times though that it would register zero, that I took zero of the meds. And I took them."*

Self-awareness of system syncing signals

Participants enjoyed the feedback of the flashing and beeping after taking their medication and felt reassured that the app was synching with the electronic pill bottle to accurately keep track of their adherence. Participants said, *(P039) "…I took my medicine,*

closed it up. And I said; okay, it's going to flash. And then when it flashed, I know it registered to my phone. So it's good to know." (P073) "I like that it lights up, and it connects to the phone, and that the phone knows you took your meds. I can see it. I can know it right away."(P033) "…listen for that click. And then you see lights flashing. And then you go back and you see the task is done." However, a few participants did not understand the connection between the device beeps/flashes after pills were taken and when to know if the bottle is working. Some participants stated, *(P004) "It's like beep-beep. Like what's that beep-beep? Confusing…" (P081) "It just, it gets me nervous sometimes because I'm not use to the flash…I'm like; where is this light coming from?"*

Bibliography of Outputs

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