Community Health Worker And MHealth to ImProve Viral Suppression (CHAMPS)

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STUDY PURPOSE AND RATIONALE

Persons living with HIV (PLWH) now achieve a near-normal life expectancy due to antiretroviral therapy (ART) which has transformed HIV from a terminal diagnosis to a manageable chronic condition.[1-4] Despite widespread availability of ART in the United States (US), many of the country's approximate 1.1 million PLWH[5]—in diverse geographic locations—are not fully benefitting from ART due to poor adherence.[6] Suboptimal ART adherence is a challenge in the US South which accounts for 51% of new domestic cases annually.[7] The Southern HIV epidemic is even more pronounced in the "Deep South"[8] with striking numbers in Alabama (AL) where PLWH experience poor viral suppression (62%).[9] Likewise, the heavy HIV burden in the US Northeast[10] is in New York City (NYC) which accounts for 82% of all PLWH in NY state.[11] Further, in the NYC region, only 67% of PLWH achieve sustained, or durable, viral suppression (the ultimate goal of ART). In response, the US government prioritized four NYC-area counties and AL (our study sites) as five of 55 areas with a substantial burden of HIV in the Ending the HIV Epidemic (EHE) plan.[12] These suboptimal HIV health outcomes occur at a time when clinicians have limited time and the US healthcare system remains fragmented,[13] further exacerbating the challenges inherent in the lives of underserved, marginalized groups, such as PLWH.[14] Therefore, the development and evaluation of interventions using a cadre of community health workers (CHW) holds promise for addressing these challenges in the US.[15, 16] Yet, research is urgently needed to bring CHW interventions to scale, particularly in EHE priority locations.

Despite efforts to achieve UNAIDS 95-95-95 targets, marked deficits remain in HIV viral suppression and ART adherence among a growing number of PLWH.[21-26] Progression of HIV disease and premature deaths among PLWH have been attributed foremost to insufficient engagement in medical care and adherence to HIV treatment regimens.[27, 28] Quick access to ART and subsequent sustained ART adherence is **central to therapeutic success** and is a critical determinant of long-term health outcomes (e.g., viral suppression) in PLWH.[29-31] 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 as a consequence of ART non-adherence may lead to emergence of drug resistance and loss of future treatment options.[32-34]Therefore, developing effective interventions to enhance ART adherence is essential.

Gaps in HIV treatment are particularly pronounced in the US South and Northeast, specifically, AL and NYC, the two high priority settings for our study. The Deep South, a colloquial term comprising nine US states, including AL, had the highest HIV diagnosis rates of any US region during the past decade.[35] In AL, HIV disproportionally affects racial minority groups with Blacks comprising 63.7% of PLWH and 73.8% of new diagnoses in 2019.[36] Poorer HIV-related health outcomes are seen in AL as compared to other regions, with higher HIV-related mortality rates,[37] higher rates of AIDS diagnoses[38] (oftentimes an indicator of late diagnosis or poor disease management[39-41]), and lower rates of engagement in HIV care and viral suppression.[42] While characteristically different from AL, NYC continues to have high HIV diagnosis rates as well.[43] HIV disproportionally affects racial minority groups in NYC, too, with Blacks comprising 43.5% of PLWH and 45.9% of new diagnoses in 2018.[44] Poorer HIV-health outcomes in the Bronx, as compared to other NYC boroughs, have been noted with higher HIV-related mortality rates,[45] higher rates of AIDS diagnoses,[43] and lower rates of viral suppression.[46]

CHW and related models have demonstrated positive impact for medication support, seeking treatment, and clinic-patient relationships. Interventions with CHW have shown promise both globally[47-49] and in the US. One study in Seattle tested the effect of a 3-month CHW intervention and found an association with greater ART adherence at post-intervention.[50] In another domestic study of an online CHW social support ART adherence intervention, substance using participants reported significantly higher overall ART adherence.[51] A small study of 20 PLWH in Kansas City, Missouri showed the positive effect of "READY," a peer-led CHW intervention for improving ART adherence in patients who had experienced repeated non-adherence.[52] Collectively, these studies demonstrate the efficacy of CHW and other peer-led interventions for improving ART adherence. In addition, CHW can interface with the healthcare system at lower costs and require less training than clinicians.[53-55] This is especially important now given the limited time of clinicians and the fragmented condition of the US healthcare and insurance system.

However, CHW models do not provide strong evidence for improving key psychosocial or HIV health outcomes associated with ART adherence and viral suppression,[56, 57] e.g., HIV-related stigma, quality of life, psychosocial distress/stress, adherence medication and skills, and adherence self-efficacy**.** Prior work in the Deep South suggests that it is the *enhanced relationship* between CHW and PLWH that is vitally important and is associated with improvements in linkage to care, retention in care, and viral suppression.[58] In our BA2C RCT, CHW delivered an intervention adapted from ARTAS, a CDC evidence-based intervention (EBI) shown

to significantly increase both linkage to and retention in care. While ARTAS was developed for new-to-care PLWH, BA2C was tailored and adapted for PLWH who had previously linked to but were not currently engaged in care. BA2C results showed that participants in both the intervention and comparison groups improved across multiple outcomes (linkage to care, retention in care, ART prescription, and viral suppression), but there was no significant difference between groups. Some of the limitations of the BA2C study included poor retention rates (70%) and difficulty attending CHW intervention sessions, suggesting that a hybrid intervention in which CHW sessions can be delivered through a mobile platform has the potential to improve the efficacy of the intervention. Given the limitations of the BA2C intervention[59, 60] and in direct response to RFA-NR-20-002, *Strengthening the Impact of Community Health Workers on the HIV Care Continuum in the US,* we will leverage our mHealth work to overcome the limitations of the BA2C study. Namely, we will use mHealth technology to overcome logistic hurdles of connecting participants and their CHW and to improve engagement through the tools in our WiseApp.

The ubiquitous nature of mHealth technologies in daily life creates opportunities for health behavior management tools that were not previously possible[61] and has the potential to address many of the healthcare needs of PLWH. The use of mHealth can reduce geographic and economic disparities and personalize healthcare,[62, 63] which is particularly relevant to PLWH since a majority represent underserved and minority groups.[64-66] mHealth technology is especially important in the context of improving ART adherence in PLWH.[67] There is preliminary evidence that mHealth technology is a feasible, attractive, accessible, and effective platform for improving ART adherence in PLWH.[68-70] Eighty-one percent (81%) of Americans are smartphone owners,[71] and our previous work suggests that this percentage is surprisingly higher with 83.7% of PLWH in Birmingham, AL owning a smartphone.[72] In NYC, smartphone ownership among low-income racial/ethnic minority PLWH is even higher with only 1.7% of participants who screened for our clinical trials (NCT03205982, NCT03182738) being ineligible because they did not own a smartphone. There is evidence that underserved populations use smartphones as their primary method for accessing the Internet.[73, 74] Finally, there is evidence that mHealth technology can promote the prevention and management of chronic illnesses such as HIV,[75] thereby allaying weaknesses of the BA2C intervention.

To that end, we developed the WiseApp using strong user-centered design research with underserved PLWH that draws on considerable formative work with PLWH, HIV clinicians, HIV case managers and the CDC (U01PS003715, PI: Schnall).[19] We then built the 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 (R01HS025071, PI: Schnall). The WiseApp is an innovative self-management tool aligned with the National Institute of Nursing Research (NINR) Strategic Plan[76] currently being evaluated in a RCT (NCT03205982) with 200 PLWH in NYC with poor ART adherence. Further details are in the preliminary studies section below. Integrating the functionality of the WiseApp to deliver the CHW intervention remotely will overcome many of the limitations of the BA2C intervention, namely attendance at in-person sessions due to scheduling, distance, or finances.

Implementation research is underutilized in HIV self-management, mHealth studies, and CHW interventions. Despite the development and well-documented success of behavior change interventions for PLWH, interventions often fail to sustain behavior change over time or demonstrate long-term efficacy.[18] mHealth technology has the potential to empower patients to self-manage a chronic condition, such as HIV.[77] However, implementation of mHealth technology is often fraught with barriers to adoption sometimes owing to a dearth of evidence related to implementation of these tools.[78] CHW interventions, too, are rarely designed, implemented, or evaluated using theory-driven implementation frameworks.[79]

Combining elements of clinical efficacy with implementation research can enhance public health impact. Implementation research is often overlooked and can be used to predict issues that may arise with the real-world implementation of an intervention. Guided by a rigorous implementation research framework, RE-AIM, we will assess the contextual factors that influence translation, adoption, replication, sustainability and implementation of *CHAMPS* across racial/ethnic groups and settings (Aim 3). *A priori* blending of clinical efficacy and implementation trials can more quickly translate research findings into routine practice[80] which can potentially yield much richer data that is especially useful to advance science and significantly impact public health. In this study, we will conduct an efficacy trial and assess implementation factors to test a clinical intervention while gathering information on its delivery and/or its potential for implementation in a real-world situation. This method will allow us to evaluate the potential strategies for ensuring widespread implementation of *CHAMPS* in future work.

In summary, this study addresses limitations in current research on CHW interventions to improve viral suppression and ART adherence. We propose to build on our strong preliminary data and directly respond to RFA-NR-20-002 by strengthening our CHW intervention (BA2C) using our existing mHealth approach

(WiseApp). Guided by a rigorous theoretical model of supportive accountability, the literature and our preliminary work support the scientific premise that adding WiseApp to the CHW intervention will enable PLWH to self-manage their ART regimens while CHW monitor their ART adherence in real-time ultimately leading to viral suppression and ART adherence. The proposed study will provide further information regarding the successful wide-scale implementation of this combination intervention in two high priority settings.

The proposed study will test the clinical efficacy and assess the implementation factors of the resultant CHW intervention, ***C**ommunity **H**ealth Worker **A**nd **M**Health to Im**P**rove Viral **S**uppression (**CHAMPS**)*, through the following specific aims with virally unsuppressed adult PLWH (n=150 in AL and 150 in NYC):

1: Conduct an RCT to assess the *efficacy* and *sustainability* of *CHAMPS* on viral suppression (primary outcome) and ART adherence (secondary outcome) compared to the standard of care (standard of care, control group) over 6 and 12 months.

PLWH randomized to CHAMPS will have significantly greater:

H_1: Viral suppression (primary outcome) than those in the standard of care group.

H_2: ART adherence (secondary outcome) than those in the standard of care group.

2: Identify mediators and moderators of *CHAMPS* on study outcomes.

*H_3: HIV medication taking self-efficacy, motivation expectancies, self-regulation skills, and HIV-related stigma **mediate** the effect of CHAMPS on viral suppression and ART adherence.*

*H_4: Depression, anxiety, and substance use **moderate** the strength of the effect of CHAMPS on viral suppression and ART adherence.*

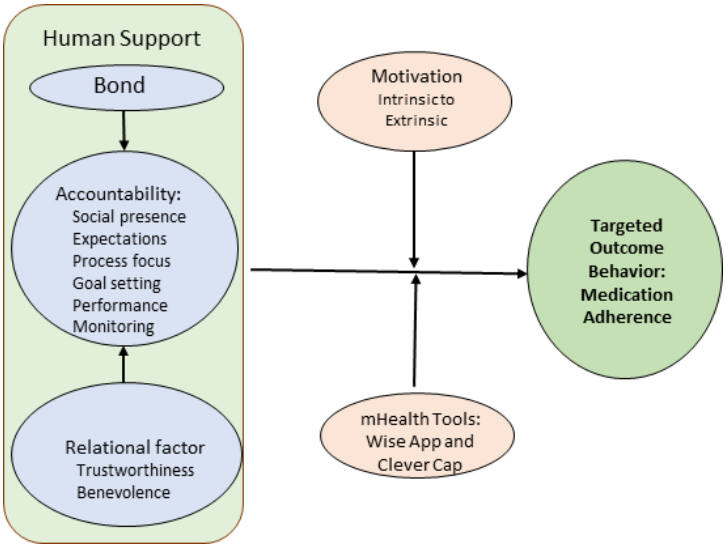
3: Guided by the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework, identify multi-level factors associated with successful implementation of *CHAMPS* to inform future implementation and scale-up.

This study seeks to expand and strengthen a CHW model through an extant mHealth approach. Findings will inform the effect of *CHAMPS* on outcomes related to the HIV Care Continuum in two EHE priority settings.

Theoretical Framework

The intervention is guided by the conceptual model of supportive accountability illustrated in **Figure 1**.[86] The model is based on the premise that human support increases medication adherence through accountability to a coach (in *CHAMPS* – a CHW) who is perceived as trustworthy, knowledgeable, and benevolent. Accountability should involve clear, process-oriented expectations guided by the patient (e.g., reporting adherence, problem-solving). The effect of accountability may be mediated by patient motivation, elicited through MI, so that patients with higher intrinsic motivation may actually require less support. The process of support is further supported by technology (WiseApp in this study) with different advantages and disadvantages for each mode. Multiple studies have demonstrated that human support is a strong predictor of viral suppression and adherence to ART.[87-89] Although overall support predicted adherence in these studies, other components of social support, such as instrumental support (i.e., practical assistance) and informational support (advice or problem-solving) offered through *CHAMPS*, are also predictive.[87] Both BA2C and WiseApp—and the proposed integrated intervention, *CHAMPS*—have been designed to validate the importance of viral suppression and ART adherence as well as to prompt problem-solving (through informational support). These interventions utilize human support to provide tailored conversations to improve both short- and long-term adherence. Social support theory also suggests that an ongoing alliance between the study participants and CHW could protect against depression, substance use, and anxiety.[90-93]

Figure 1. Model of Supportive Accountability



Preliminary Data: We have conducted two studies to support the use of this intervention.

1) **Birmingham Access to Care (BA2C)**. BA2C (funded by AIDS United, Co-Is: Batey and Mugavero) was a single-site RCT conducted between July 2013 and February 2016 in partnership with Birmingham AIDS Outreach (BAO)

and the University of Alabama at Birmingham (UAB) 1917 HIV Clinic. The study focused on re-engagement to care among PLWH who had previously linked to care but who were not currently engaged at the time of the study (N=170). The BA2C intervention was based on a CDC-recognized EBI, ARTAS, which was the first RCT shown to significantly increase linkage to and retention in care among recently diagnosed PLWH.[17, 82, 83] The ARTAS intervention consists of a brief, strengths-based case management/MI approach aimed at facilitating a close, supportive relationship between the CHW and participant and consists of up to five visits. BA2C, which was tailored and adapted to PLWH who dropped out of care, expanded on ARTAS to provide additional support over a longer period. Participants enrolled in the intervention arm received an initial face-to-face meeting with an assigned CHW prior to attending their first return HIV primary care visit and attended at least ten and up to 12 visits over six months in which the CHW worked collaboratively with participants to resolve any barriers to care. Depending on participant needs, the CHW may attend medical appointments with the participant and/or provide transportation. Participants in the control arm received standard of care. Study findings from BA2C showed that participants in both study arms improved across multiple outcomes (linkage to care 30 days after baseline; retention in care, ART prescription, and viral suppression at 12 months after baseline), but there was no statistically significant difference between groups. The lack of statistical significance was likely due to a small sample size and a 70% retention rate due to challenges participants had in attending study appointments. *CHAMPS* will build on the evidence-based premise of BA2C and the enhanced relationship between CHW and participants while adding an mHealth component to facilitate study retention, described below.

2) **WiseApp** is derived from formative work funded by and in collaboration with the CDC (U01PS003715) to design a self-management app for PLWH[84] with the goal of being more widely applicable across 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 (ISR) framework and incorporated end-user feedback throughout the design process.[85] 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 (See Figure 2). A key component of WiseApp is a medication tracker linked to an electronic pill bottle and a capability to link to a fitness tracker and monitor physical activity. WiseApp 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. Additional images of the WiseApp are found in Table 2. The WiseApp is aligned with the NINR Strategic Plan[76] and is currently being evaluated in an RCT (NCT03205982) in 200 PLWH with poor ART adherence in NYC (R01HS025071, PI: Schnall). Preliminary data show evidence for the success of this intervention in comparison to the control group for improving ART adherence (primary outcome) (58% ART adherence, 47% ART adherence, respectively, p=0.03) in low-income racial and ethnic minority PLWH (mean age=49.1 years, SD±10.6).

Figure 2. Sample Image from the WiseApp

List of currently prescribed medications

STUDY DESIGN

Aim 1: Assess the efficacy and sustainability of *CHAMPS* on viral suppression (primary outcome) and ART adherence (secondary outcome) compared to the standard of care (standard of care, control group) over 6 and 12 months.

Design Overview

A randomized controlled trial will be conducted with 300 PLWH (n=150 in AL and 150 in NYC) over 12 months. Participants will be randomly assigned to CHAMPS (intervention) or a standard-of-care control arm.

Intervention Arm. The CHAMPS intervention, outlined in Table 1, is a 6-month intervention guided by BA2C.[17] The CHW will be demographically-matched to our study participants.

Table 1. Components of CHAMPS delivered over the 6 month intervention period

10 sessions with the CHW	Detailed in **Table 3** below
CleverCap	Participants and CHW will be able to track ART adherence.
WiseApp	• CHW will be able to deliver sessions to the study participants through the WiseApp. • Participants will be able to self-manage their health through the content described in **Table 2**. • Participants and CHW can securely chat with one another.

Intervention Training and Support. The CHW will be trained on the intervention: content of each session, MI, strengths-based case management, ARTAS,[17] HIV and substance use, and safety in the field. The CHW will also be trained on use of the WiseApp and CleverCap assuring all study participants and CHW are able to successfully use the mHealth technology. Training for the CHW will also be provided on: human subjects research protection, financial conflict of interest, HIPAA, and data privacy and security. The CHW will engage in supportive strengths-based case management and MI with the study participant. Intervention visits (~ten over a six-month period) will help participants access primary medical care by acknowledging and addressing barriers to care. Participants will have the option to participate in most CHW sessions in-person or via the App. This will help participants overcome many of the challenges to participating in-person, which was a frequent barrier in Birmingham and a current barrier due to COVID-19 in NYC.

The WiseApp offers the following functionality listed in Table 2, and the CleverCap is linked to the WiseApp. The CleverCap fits on standard pill bottles, dispenses only the prescribed amount of medication, keeps track of medications dispensed, and communicates wirelessly with mobile devices. Participants are then able to self-monitor their medications, and the CHW will also be able to track study participants' adherence to their ART medication in real time. Participants receive reminders through the WiseApp when they have not taken their medication on time and receive encouraging messages (e.g., Great job! You've met your goal for not forgetting your meds) when they have taken their medication. Communication, whether in-person or via the App, will enhance the relationship between the CHW and the study participant.

The sessions and sample content are illustrated in Table 3. CHAMPS is a manualized intervention and study visits focus on topic areas such as linkage to care, medication adherence, health literacy, access to support services, and HIV disclosure. Ideally session #1 will be in person and #6 needs to be in-person during the care visit.

The remaining visits can be in-person or through the WiseApp. The CHW maintains consistent communication with the participant to make sure the participant's needs are addressed. Upon assignment to the intervention arm, a CHW is assigned to and meets with the participant as soon as possible, generally on the same day but no more than five business days. The WiseApp has a communication feature which will allow the CHW to deliver most of the sessions described in Table 3 remotely.

Table 2. WiseApp Features used for CHAMPS intervention

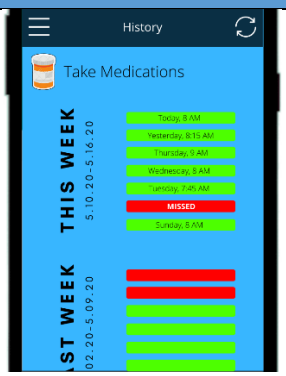
WiseApp Feature	CHW Integration	WiseApp Screen-shot
Medication Tracking	Participant and CHW monitor medication adherence. Participants receive reminders when they have not taken their medication on time.	
CleverCap	CleverCap syncs with the WiseApp to record medication adherence.	
Chat	1:1 chat for participant and CHW for individual conversations, allowing CHW to provide intervention sessions.	
Testimonials of Lived Experiences	Stories of CHW's experiences living with and/or supporting PLWH.	

Table 3. Outline of CHW Sessions with study participants guided by BA2C and ARTAS content		
	Title	**Sample Content for Each Session**
1	Building the Relationship	Introduce the goals of *CHAMPS*
2	Introduction to the WiseApp	Discuss how the App can be used to facilitate communication between the CHW and the provider. Review the medication tracking function and how this can be used by the CHW and the participant.
3	Emphasizing Personal Strengths	To help the patient self-identify personal strengths, abilities, and skills.
4	Learning to Make Contact	Assist patient in preparing a list of questions to ask care provider
5	Reminder Call	Call at the agreed upon time; Remind participant of any needed documents
6	Primary Care Provider Appointment #1	Support patient's efforts during care provider visit
7	Debriefing Provider Visit with Client #1	Solicit patient's input on what went well for the patient. Elicit from the patient what he or she learned from the care visit and what strengths he or she demonstrated during the care visit.
8	Reviewing Progress	Plan for and review the transition process between the CHW and study participant
9	Debriefing Provider Visit with Client #2	Solicit patient's input on what went well for the patient. Elicit from the patient what he or she learned from the care visit and what strengths he or she demonstrated during the care visit.
10	Completing the work	Review the transition process/ Transition to long term/Ryan White case manager or other providers

Standard of Care (Control Arm)

The control condition includes standard health services offered at each site (e.g., mental health services, case management, referral to clinical care) and a brief adherence educational session. The standard educational session consists of a review of medications and recommended dosing (i.e., to understand regimen), adherence expectations, toxicity expectations, and medication misperceptions. During the educational session, participants can ask questions and receive answers to reinforce their current ART regimen. All participants receive referrals to mental health, drug/alcohol treatment, and/or other HIV services as necessary. In summary, standard of care at each of the sites is comprehensive (far more extensive than standard of care for the general non-HIV infected population) and follows the Department of Health and Human Services HIV guidelines.[113] All sites also provide mental health and psychosocial support services.

Eligibility Criteria for Participants

Inclusion criteria:1) Able to speak, read, and write in English or Spanish (at the New York City site only); 2) Aged ≥18 years; 3) Willing to participate in any assigned arm of the intervention; 4) Having been diagnosed with HIV ≥6 months ago; 5) Have an HIV-1 RNA level >200 copies/mL, or at least one "no-show" visit in the past 12 months, or report either not virally suppressed in the past 12 months or virally unsuppressed in the past 12 months; 6) Own a smartphone; and 7) Ability and willingness to provide informed consent for study participation and consent for access to medical records. *Participants are not eligible if they meet any exclusion criteria:* 1) Reside in a nursing home, prison, and/or receiving in-patient psychiatric care at time of enrollment; 2) Terminal illness with life expectancy <6 months; and 3) Planning to move out of the area in the next 12 months.

Inclusion consideration: We carefully considered including newly diagnosed patients (diagnosed <6 months) and have chosen to not include this subset of PLWH because: 1) Our piloted interventions did not include newly-diagnosed persons; 2) Newly-diagnosed individuals are treatment naïve and their adherence behaviors are unknown and may change frequently as they begin their ART regimen; and 3) The advent of rapid-start ART for newly-diagnosed individuals is currently under trial in both locations, providing an ART-initiation intervention for these individuals that could compromise our study results.

Recruitment Plan

We will enroll a minimum of 50% women or transgender women combined across sites and stop enrollment of men at 150 to meet this goal. We will track the reasons and demographic characteristics of those refusing to participate and examine those data as part of our ongoing monitoring and implementation evaluation activities (see Human Subjects).

We will use the following strategies for recruiting PLWH for all aims of the study; these approaches have been successfully used by our team in past studies.[94-98] Planned offline and online recruitment venues include the following:

- Clinic and Community Outreach: Clinic social workers and peer outreach staff will distribute information about the study using flyers and electronic advertisement boards in clinic waiting rooms.
- Community Presentations: Across sites, study staff will attend and/or make study presentations at selected activities and social events sponsored by community partners, e.g., community advisory boards, health

fairs, and clinic/organization staff meetings. When making presentations, the presenting recruiter will provide a brief study background and invite all interested potential participants to speak to one of the study recruiters.

- Social Networking Websites and Apps: We will recruit participants online through various websites and apps. We will use psychographic targeting (i.e., in-depth, publicly available consumer data such as interests, city) to advertise to potentially eligible individuals in the two cities.

Consistent with the multi-pronged recruitment approach designed to reduce recruitment bias[99, 100] and to minimize potential recruitment problems, our team will carefully monitor each approach. This will involve weekly review of recruitment data with staff to assess efforts. In this way, recruitment will be a dynamic process and will reach the proposed diverse group of PLWH.

Sex and Race/Ethnicity Considerations: The HIV literature is limited in interventions among women and racial/ethnic minorities.[102] Drs. Schnall and Batey have successfully recruited many African-American, Latino, and female PLWH.[103-106] We plan to enroll a minimum of 50% African-American, Hispanic, Asian, and 50% female participants, resulting in representative findings. Sex as a biological variable will be analyzed as a potential effect-modifier in our outcomes. Data will be sex-stratified to explore sex-specific responses as an exploratory analysis (e.g., not powered to detect sex-specific differences in outcomes).

STATISTICALPROCEDURES

Sample Size and Power Calculation

We have estimated the statistical power for the primary outcome of viral suppression (viral load **≤** 200). We will recruit and enroll 300 participants (n=150 in each site) and use a 1:1 random assignment to the intervention arm and the control arm (i.e., 75 in each arm per site). We estimate the statistical power to examine efficacy of the intervention at six months for the total subjects. All power estimations are based on α=0.05 and 2-sided tests and following assumptions: (1) an 80% retention rate, at each follow-up assessment for each study arm (based on our 86.1% retention rate in New York City WiseApp trial); (2) a correlation of 0.6 of outcome measure for participants at different time points of assessment; (3) an intra-cluster correlation (ICC) of 0.2 of participants of same study sites; and (4) 75% baseline viral suppression rate (based on preliminary data of the BA2C study).

For the total sample (n=300), the proposed study will have at least 80% power to detect a difference of 12% or greater in viral suppression. The 12% difference in viral suppression is equivalent to a small effect size (Cohen's D of 0.31). Therefore, the proposed study will have sufficient power (≥80%) to detect a small effect size or greater. Based on findings from our BA2C and WiseApp interventions, we expect a combined improvement of 12% on viral suppression as compared to the control arm.

We have also estimated the statistical power to assess sustainability of the intervention at 12 months. For this analysis, we will conduct a non-inferiority test of viral suppression at Month 12 as compared to Month 6. This study will have at least 80% power to conduct a non-inferiority test with a margin of 10%.

Sampling approach to successfully enroll PLWH who are not optimally engaged in HIV Care: Using active and passive recruitment methods, the project coordinator at each site will oversee and participate in recruitment efforts. The study staff hired through this project and the peer-to-peer networking efforts at each site will be used to recruit study participants. Our study team at both sites has extensive experience in recruitment efforts for projects similar to the one proposed here and will be able to successfully recruit the study sample.

Eligibility Screening

Potential participants will either call, text, or email the study team via the advertised phone number or email address or, if contact information is gathered at the recruitment venue, be called, texted, or emailed by project staff. Screening will be conducted over the phone, in person for walk-ins, or electronically via REDCap. Each potential participant will be screened for eligibility based on the inclusion/exclusion criteria. Participants who do not have a recent (≤8 weeks) available viral load test result will need to complete a study blood draw. Participants may also sign a Release of Information (ROI) form, in-person or remotely, to allow study staff to access their electronic medical record (EMR) and determine eligibility based on past "no-show" visits. Forms completed electronically will be conducted via video conferencing such as Skype, Zoom, FaceTime using REDCap to collect the e-ROI and answer participant questions. Through the REDCap platform, participants will

be able to securely download a copy of the e-ROI for their records. As part of the REDCap e-consent platform e-ROIs will be automatically archived and securely stored in REDCap. If deemed eligible, staff will work with thepotential participant to schedule an enrollment visit at a convenient time for the participant.

Randomization

Using the randomization approach described below, there will be random or minimally biased assignment of subjects to study arms. Randomization will be achieved through a blocked design utilizing permuted blocks of random sizes. The design ensures equal representation of treatment assignment across groups and protects the study team and investigators from easily anticipating treatment allocation.[107-110] Randomization to *CHAMPS or* standard of care is 1:1. Participants will be randomized using computer-generated random numbers at baseline. The randomization database will be stored on a password protected computer at Columbia University and will only be accessible to MPI Schnall to avoid the possibility of the study sites subverting randomization as has been noted in previous studies.[111] Following completion of the informed consent and baseline assessment, participants will be randomly assigned to one of two trial arms using sequentially numbered, opaque, sealed envelopes containing the intervention assignment, which the staff member opens at the moment of randomization.[112]

Procedures

Upon arrival at the screening visit, we will collect written informed consent prior to enrolling into the study trial (See Protection of Human Subjects). The informed consent form provides details of the study procedures, risks, benefits, site contact information, and the nature of confidentiality and voluntary participation. The consent process also covers information on the trial and compensation for time.

Participants in both the intervention and control arms will visit the study sites (BAO/1917 Clinic-AL and Columbia University School of Nursing–NYC) at the screening, baseline, 6, and 12-month visits. Following the completion of the baseline study instruments, study participants in the CHAMPS intervention arm will be given a CleverCap™ Lite dispenser and trained on how to use it; they will also be trained by study team members on how to use the different features of the Wise App and receive medication reminders. Upon assignment to the intervention arm, a CHW is assigned to and meets with the participant as soon as possible, generally on the same day but no more than five business days. The CHW will deliver the interventions outline in Table 3 either in-person or remotely throughout the course of the study.

Participants will be texted appointment reminders for study visits. Hard to reach participants will also be sent scheduling reminders. These reminders will be sent via Qualtrics, REDCap and/or encrypted e-mails from the study's secure CUMC e-mail address.

Participants in both arms will receive $40 at baseline, $50 at 6-months, and $60 at 12-months as a token of appreciation for their time participating in the study visits and for their blood draws. Participants who complete Qualitative Interviews will be compensated $40 for completing that interview.

Overview of Data Collection Time Points

Follow-up visits will be scheduled 30 days before to 30 days after the target window based on participant availability and site capacity. Timing of follow-up visits is scheduled to allow site flexibility while still scheduling follow-up visits within a reasonable time span.

Sound Retention Efforts

Using the retention efforts described above and in the Recruitment and Retention attachment, we are confident that we will retain at least 80% of our study sample at the follow-up assessments as we have done previously.[114]

Data Management

Data will be electronically collected, managed, and secured using REDCap™ by study staff trained on REDCap data entry, management, and security.[125] Quality assurance measures, including built-in skip patterns, validation ranges, and logic checks, minimize data collection and data capturing errors. Quality control measures, including internal monitoring systems and daily and weekly reporting, are run to ensure expedient error correction and to optimize data integrity.

Study Outcomes

The study outcomes are described in Table 4**.** The primary outcome of the study is viral suppression which will be operationalized as viral load ≤200 at 6 months. Viral load is the biologic correlate of the ART adherence behavior; yet, to achieve biologic change, there must be change in the adherence behavior. As suggested through the "Undetectable equals Untransmittable," or "U=U," public health campaign,[126, 127] PLWH who take ART as prescribed and achieve and maintain viral suppression have effectively no risk of sexually transmitting the virus to an serodiscordant partner.[126] Our secondary and related outcomes include ART adherence measured in two ways: 1) a single-item self-report measure, an empirically validated instrument,[101] and 2) electronic pill bottle data, collected via the CleverCap bottle. The electronic pill bottle data provide a less subjective measure as compared to self-report. We will also measure missed healthcare visits using electronic medical record (EMR) data.

Table 4. Measures and Schedule of Events

	Screening	Baseline	6 mos	12 mos
Sociodemographic:(e.g., age, race/ethnicity, education, housing)		X		
Primary Outcome Measures				
Viral Load through a blood draw	X		X	X
Secondary Outcome Measures				
ART adherence (SRSI)[101] and the CleverCap (intervention group only)	X		X	X
Additional Outcome Measures		X	X	X
Quality of Life (PROMIS-29)[115]		X	X	X
HIV Symptom Index [116]		X	X	X
Engagement in HIV Care [117]		X	X	X
Mediators				
The HIV Medication Taking Self-Efficacy Scale		X	X	X
Motivation and outcome expectancies of ART adherence are assessed as three separate dimensions: attitudes, norms, and behavioral intentions to adhere to ART medication[118]		X	X	X
Self-regulation skills, which include self-monitoring, goal-setting, and enlistment of self-incentives/plans[119]		X	X	X
HIV-regulated Stigma[120]		X	X	X
Moderators				
Alcohol, Smoking & Substance Involvement Screening Test (ASSIST)[109]		X	X	X
Depression and Anxiety (Beck Symptom Inventory) [121-124]		X	X	X

Limitations and Considerations of the Study Outcome. We recognize that all the approaches for measuring viral suppression and ART adherence are limited. First, viral suppression does not directly measure a behavioral outcome but, rather, the biologic effects of the behavior. Second, the self-report measure is biased and has ceiling effects. Finally, the electronic pill box is limited to data collected from the intervention group. While this is a limitation, providing the electronic pillbox to the standard of care (control group) is likely to bias our intervention effects since this pillbox will, in fact, have intervention effects as we have found from our preliminary findings from our WiseApp trial. We closely considered each of these limitations and have, therefore, decided that this three-pronged (i.e., viral load, self-report, and electronic pillbox) approach which will provide the most rigorous approach to measuring our primary and secondary outcomes of viral suppression and ART adherence.

Mediators

Several mediators are hypothesized to explain the mechanisms through which the intervention is anticipated to improve viral suppression. Hypothesized mediators include: self-efficacy, motivation expectancies, self-regulation skills, and HIV-related stigma. The HIV Medication Taking Self-Efficacy Scale is also used to measure ART adherence self-efficacy, or the confidence to take medications in various situations.[128] Motivation and outcome expectancies of ART adherence are assessed as three separate dimensions: attitudes, norms, and behavioral intentions to adhere to ART medication.[118] Self-regulation skills, which include self-monitoring, goal-setting, and enlistment of self-incentives/plans, are also assessed.[119] In prior studies of ART adherence, HIV-related stigma and discrimination have been strongly associated with non-adherence;[14, 129] thus, we also measure HIV-related stigma.

Moderators

Several moderators are hypothesized to affect the strength of the intervention to yield improvements in viral suppression and will be explored. Hypothesized moderators include: depression, anxiety and substance use.

Depression and anxiety will be measured through the Brief Symptom Inventory, a multi-item scale of mental health in the last seven days that gives a global index and nine primary symptom domains, including depression and anxiety (α>0.80). Problem alcohol and drug use are also assessed with the Alcohol, Smoking & Substance Involvement Screening Test (ASSIST).[130] The ASSIST consists of nine items, covering ten substances (used in the past four months), including: tobacco, alcohol, cannabis, cocaine, stimulants, inhalants, sedatives, hallucinogens, opioids, and other drugs. The ASSIST assesses frequency of use and associated problems for each substance with good to excellent reliability and validity.

Other Important Outcomes

Quality of life will be measured through the PROMIS-29, an NINR Common Data Element, and an instrument which was validated by Dr. Schnall for use with PLWH.[115] HIV symptoms and management will be measured with the HIV Symptom Index[116] and Engagement in HIV Care[117] will also recorded at all assessment points. The blood draw at baseline will also be tested for genotyping, GSA chip and qPCR, hormone blood levels (Estrogen and FSH), and cytokine blood levels (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, TNFα, and CRP). The genotyping with GSA chip and qPCR, cytokine blood level and CRP, and hormone blood tests will only be collected once during the course of the study, at Baseline or at the 12-month follow-up if not completed at Baseline. The genotyping, GSA chip and qPCR will be performed by the Feinstein Institute for Medical Research at Northwell Health.

Data Analysis

The distribution of all variables will be assessed, as will the correlations between all variables and the primary/secondary outcomes. We will assess for patterns of missing data, which are expected to be low as the study utilizes computer-assisted self-interview (CASI) for sensitive data, which reduces participant nonresponse. The primary anticipated reason for missing data is attrition due to loss to follow-up. Based on our preliminary studies, we are accounting for 20% attrition from randomization to the 12-month assessment.

All multivariate analyses will be preceded by standard descriptive bivariate analyses to describe key variables and relationships among them. These analyses will include means, frequency tables, histograms, and examination of distributions. All statistical tests will be two-sided tests with the level of significance at 0.05. The primary hypothesis 1 will be a comparison of viral suppression (primary outcome) between CHAMPS and standard of care. We will also compare the drop in viral load (measured in logarithmic scale with base 10) between the two groups. Our secondary and related outcome is ART adherence measured in two ways: 1) a single-item self-report measure, an empirically validated instrument (SRSI)[101] and 2) electronic pill bottle data which we will be collecting in the intervention group since all participants will receive a CleverCap bottle for their medications. All the analyses will be based on initial assignment to groups, using the intention-to-treat principle.[131, 132]

The primary hypothesis 1 ($\underline{H_1}$) will be tested using a generalized linear mixed model (GLMM) with logit-link function for binary outcomes (i.e., viral suppression) or a linear mixed model (LMM) for continuous outcomes (i.e., viral load measured in logarithmic scale) to account for the non-independence of repeated measurements within individuals.[133] The models will include a random intercept and fixed effects for intervention group, time, and interaction term of group and time which is for testing efficacy of the intervention. The model may include stratification variables, such as study site, age, and sex as covariates. A site by group interaction will be also examined and included in each model (above) if significant at the .05 level. All analyses will be tested for goodness-of-fit using the Wald-type test, which shows satisfactory performance for models with fewer (<5) covariates.[134] A similar GLMM will be used to test sustainability of the intervention at month 12. For this analysis, we will conduct a non-inferiority test[135] to compare viral suppression rate between month 12 and month 6. For primary hypothesis 2 ($\underline{H_2}$)**,** testing for intervention effect on ART adherence measured by SRSI (secondary outcome), we will use a similar LMM as mentioned above. For electronic pill bottle data in the intervention group, we will also examine the trend of electronic pill bottom data over time with a GLMM which will include a first-order autoregressive (AR1) covariance structure, as described by Hedeker and Gibbons.[133] We will also aggregate the electronic pill bottle data at different time points (0, 6, and 12 months) and examine the association between the election pill bottle data and ART adherence data measured by SRSI using Spearman nonparametric correlation.[101] Similar GLMMs or LMMs will be used for secondary outcomes, with GLMMs for binary outcomes and LMMs for continuous outcomes.

Aim 2: Identify mediators and moderators of CHAMPS on study outcomes.

Data Analysis

Mediators. If the intervention arm shows improved viral suppression in greater magnitude than the standard of care, we will explore the extent to which this relationship works through several possible mediators, including: self-efficacy, motivation expectancies, self-regulation skills, and HIV-related stigma. For mediation analyses, we will employ MEDIATE procedures.[130] MEDIATE estimates the total, direct, and indirect effects of causal variable(s) (xlist) on the outcome variable (yvar) through a proposed mediator variable or set of mediator variables (mlist), controlling for (optional) one of more variables in (covlist). MEDIATE is similar to INDIRECT[136] but allows multiple variables and also offers features for handling and coding a single multi-categorical variable. Inferences for indirect effects can be based on either percentile bootstrap confidence intervals or Monte Carlo confidence intervals. For effect modification analyses, we will add interaction terms one-by-one for the intervention condition and the potential moderators (e.g., depression). Significant or large interaction terms suggest that the effects of the intervention differ for different subgroups, as defined by the moderators.

Moderators. In addition, we will study the moderators of treatment effect. This is a potentially impactful goal, given the gradual but assured paradigm shift in behavioral interventions from a "one-size-fits-all" approach to modern personalized medicine. Potential moderators in the current context are depression, anxiety and substance use. Regression analysis including potential moderators in the model as interaction terms will be conducted. If any interactions are significant, then patient characteristics can be used to better inform dissemination of this intervention. Moderation analysis will be performed using the R software package qLearn.[137]

*Missing data***.** Missing data may occur in the proposed study in several ways. First, it may occur due to item non-response. When missing data is limited to only a few items on a measure, we will prorate total scores for a measure by taking an average score on the measure and multiplying it by the total number of items in the scale. Missing data can also occur from attrition due to missed assessments or dropout from the study. Prior to performing any outcome analyses, we will evaluate the amount, reasons, and patterns of missing data. If the reason for missing data is not related to the outcome of interest, then they are considered to be missing completely at random, and complete case analysis will still generate unbiased estimates.[138] We will conduct sensitivity analyses to compare estimates of treatment effects with and without multiple imputation to assess the effect of missing data on statistical inference.

Aim 3: Guided by the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework, identify multi-level factors associated with successful implementation of CHAMPS to inform future implementation and scale-up.

Overview

We will use a mixed-methods, multi-stakeholder (i.e., patients, clinic and CBO staff and clinicians) process evaluation using a theory-based model for implementation evaluation (RE-AIM) to understand the barriers and facilitators to *CHAMPS* implementation. We will work with study participants, clinic, and CBO staff and clinicians to better understand how we can disseminate this CHW intervention more broadly and how this can be implemented as part of the HIV care delivery in the clinic setting, attending to nuances at our geographically diverse study sites. To that end, we have focused our RE-AIM analysis on factors which are unique to widespread implementation with a focus on predisposing, enabling, and reinforcing factors to program implementation[139] as well as paradata to better understand study participants use of the app. MPI Schnall has conducted extensive implementation analysis of her eHealth and mHealth interventions by examining these factors.[140-143] MPI Batey has conducted implementation work around the acceptability and feasibility of a workshop intervention to reduce HIV-related stigma among healthcare workers in AL and Tennessee,[144] and he currently collaborates with Co-I Mugavero on implementation evaluation of a clinic-wide risk stratification with enhanced personal contacts for retention in HIV care at seven clinics in AL.[145] Additionally, we have consulted extensively with Dr. Smith (consultant), an implementation expert,[146-150] on the development of the

Table 5. Summary of RE-AIM Dimensions and Measures	
Study Questions	**Methods, Variables, & Measures**
Reach: The absolute number, proportion, and representativeness of individuals who participate in the CHAMPS Trial.	
What percentage of the study participants use the intervention?	% and characteristics of PLWH randomized to *CHAMPS* who use the intervention; Comparisons on sociodemographic variables of users and non-users among those randomized to *intervention arm*
What percentage of the CHW visits did study participants attend in person or through the App?	% and characteristics of PLWH randomized to *CHAMPS* who attended their CHW visit
Were participants representative of target population?	% and characteristics of eligible participants who joined the study and those who didn't; Sociodemographic comparisons between *CHAMPS* participants and eligible study participants who did not join the study
***Efficacy:* The impact of an intervention on outcomes including potential negative effects, quality of life.**	
Did the intervention achieve primary and secondary outcomes?	Between-group comparisons on primary and secondary outcomes (Aim 1)
Did it produce unintended adverse consequences?	Review notes from participant study withdrawal, Notifications to the IRB about participant complaints
What effect did the mediators and moderators have on the primary and secondary outcomes?	Data analyzed in Aim 2
***Adoption*: The absolute number, proportion, and acceptability of *CHAMPS*; proportion of eligible patients that enroll.**	
Did the intervention help the organization address its mission, values, and priorities?	Key informant interviews with clinic staff, research staff, CHW, and administration - descriptive, interpretative analysis for key themes
Implementation: At the setting level, includes consistency of delivery and predisposing, enabling, and reinforcing factors. At the individual level, implementation refers to individual's use of strategies.[152]	
Were intervention components delivered as intended?	Paradata Analysis –App use by component
What barriers to implementation were identified and how were they addressed?	Key informant interviews with study staff; In-depth interviews with study participants. - descriptive,interpretative analysis for key themes
What enabling (facilitating) factors were required to support the intervention?	Project meeting minutes
	Interviews with stakeholders
***Maintenance*: Individual – Understanding Use of the App over time.**	
Did the intervention produce lasting effects at individual level?	Long-term efficacy of *CHAMPS* intervention over 12 months
Is there the potential for sustaining *CHAMPS* over time?	Key informant interviews with clinic staff, research staff, CHW and clinicians, CBO staff and study participants.
How did the intervention evolve?	Project meeting minutes; *Paradata*

implementation evaluation for this proposal; Dr. Smith will provide oversight, along with MPIs Schnall and Batey, for all implementation activities.

Process Evaluation Outcomes

The RE-AIM evaluation dimensions and associated measures in our study are summarized in Table 5. In addition to testing the **E**fficacy of *CHAMPS*, we will concurrently measure the four remaining RE-AIM dimensions[151] as follows:

Reach –1) percent and demographic and clinical characteristics of those who joined the study based on the current national statistics of PLWH, and 2) percent and demographic and clinical characteristics of those randomized to the intervention who attended visits with the CHW and who used the App compared to those who did not.

Adoption – We will recruit a random sample of study participants post-intervention to assess acceptability and perceived usefulness of *CHAMPS* (see Sample Interview Guide – Table 6) and recruitment logs to calculate the percent and representativeness of patients that agree to participate in the study. Interviews will be collected until saturation is reached, but we estimate a total of 60 participants (40% of study sample).

Table 6. Follow-up Sample Interview Guide
• Describe your general perceptions of *CHAMPS* and its usefulness for helping with ART adherence. • How helpful was *CHAMPS* for improving your ART adherence? • How helpful was *CHAMPS* for improving your viral suppression? • What would you change or improve about *CHAMPS*? • How did *CHAMPS* help you gain information about your ART adherence? • How did *CHAMPS* help you gain information about viral suppression? • How comfortable were you in using the App in social settings? Probe: where and when did you use it mostly?

- How often did you use the App in a typical week? Would you recommend it to a friend?
- Did you stop using the App altogether at some point? (If yes) Why?
- Describe the usefulness of the reminders to take your medication and attend the meeting with your CHW.
- Is there the potential for sustaining *CHAMPS* over time (clinic administration)

Implementation and Maintenance will be evaluated through interview data with the study participants (N=60) and clinic staff and research staff (N=15), CHW (N = 2 Birmingham, 2 NYC), and clinic administration (N = 2 Birmingham, 2 NYC) (Table 6). We will use post-intervention testing interviews with study participants and clinic administration and staff to assess acceptability and perceived usefulness of the *CHAMPS* intervention at the 6-month and 12-month follow-up timepoints. 30 participants will be randomized for interviews at each time point; each site will conduct 15 interviews per time point. Interviews will be collected until saturation is reached. All in-depth interviews will be audio-recorded with two digital recorders to safeguard against mechanical failure. The study team will also take field notes. Participants will be compensated $40 for completing these interviews.

At the individual level, we will understand participants' use of the App over time through the collection of paradata[153] (Table 7). Paradata is considered "free" in that it does not require any additional effort from the user.[154] To explore barriers and facilitators to widespread implementation of *CHAMPS*, we will collect data during the intervention, implementation, and after the trial has ended.

Table 7. Paradata Collected for Each App Use

1. Unique Code
2. Page accessed
3. Time stamp
4. Device Type

Data Analysis

Quantitative Data Analysis of RE-AIM Dimensions

We will use descriptive statistics to characterize process evaluation outcomes around RE-AIM (e.g., Reach: penetration; Adoption: representativeness of persons living with the disease). We will examine Reach and Implementation as a function of individual (e.g., perceptions of barriers to care) and organizational level factors (e.g., provider type). Variance components analysis[155] on Reach and Implementation outcomes will be used to determine the relative percentages of the overall implementation variability being introduced at each level. Multi-level regression models[156] will be employed to assess the unique contribution of individual-level factors on outcomes.

Paradata Data Analysis

The primary paradata that will be collected is shown in Table 7. From this data, we will derive the following use of data for each session: duration on each page, page progression through the application, time from login to result, and total time from login to logout. We will analyze the data on multiple scales and perspectives: individual-level (i.e., user-level), application-level, page-level, session-level, and how these differ by demographic characteristics, technology use, and outcomes measures. Additionally, we will measure the amount in bytes of user data transmitted. Importantly, longitudinal analysis will determine if user-experience changes with repeated use. The paradata collected from each page will be analyzed to generate a "heatmap" of user-interaction (i.e., the distribution of activity for each link/button). Use of the heatmap will inform user duration on each page of the application and user interaction with the app content, the contact pages, and the help page. We will explore usability issues with consideration for how many times users accessed help and what page of the app referred them to the help, implying the need for clarification. We will analyze differences in the aggregated data by demographic group (e.g., age) to allow us to better understand engagement with the intervention and potential facilitators and barriers to App use.

Qualitative Data Analysis of Interview Data

The study team will meet and review transcripts and notes from the interviews. Drs. Schnall, Batey, and Kay[143, 157-163] have extensive experience in qualitative analysis and will work with two research assistants to code the transcripts. Field notes and transcripts will be analyzed by the researchers using NVivo™ (QSR International, Victoria, Australia) software. Participants' statements will be captured using memoing and then sorted into the categories of interest. Open coding will be used to develop initial data categories. Some codes will be derived from the questions included in the interview and other codes will emerge from themes and patterns identified in the narratives. An initial set of codes will be independently generated by two coders. Codes will then be compared and synthesized to result in shared coding categories and sub-categories, all with definitions, inclusion and exclusion criteria, and examples. Coders will discuss discrepancies until they reach consensus. Findings will guide modifications of *CHAMPS*, if warranted.

Scientific Rigor: The team will adhere to qualitative research processes to ensure the credibility, confirmability, dependability, and transferability of the qualitative data from these analyses. To support the credibility of the data, we will conduct peer debriefing. We will also use "member checks," i.e., sharing of initial data

interpretations with participants to ensure accurate interpretations. Triangulation of findings, along with reflexivity, will enhance the confirmability of the interpretations. The investigators will carefully record an audit trail and keep extensive field notes to facilitate transferability of study findings into other contexts.

RISKS, BENEFITS & MONITORING

Risks to Human Subjects

Research Environment and Commitment to Protection of Human Subjects:

Columbia University Irving Medical Center (CUIMC), Birmingham AIDS Outreach (BAO), and University of Alabama at Birmingham (UAB) are committed to safeguarding the rights and welfare of human subjects in all research activities, and all have a current Assurance of Compliance with the Office for Human Research Protections (OHRP). The investigators will follow all required policies related to the protection of human subjects. All investigators have fulfilled human subjects protection and Health Insurance Portability and Accountability Act (HIPAA) training requirements (including CITI basic and refresher courses, Good Clinical Practices, and conflicts of interest) and are up-to-date with these certifications. The study described in this application will be reviewed and approved by Western Institutional Review Board (IRB), and we will seek reliant review at UAB and BAO (to fulfill the single IRB policy) prior to any participant recruitment or data collection activities. All prospective participants will be fully informed of the intent of the study and expectations of participants prior to enrollment using an IRB-approved informed consent form.

Human Subjects Involvement, Characteristics, and Design

Characteristics of the Population:

The trial will involve the recruitment and retention of men and women (*n*=300) with HIV infection who are virally unsupressed in New York City (NYC) and Birmingham, Alabama. Study volunteers must meet general criteria to be eligible for further screening for participation in the study. In most cases, this information will be acquired during a telephone interview prior to a screening/consent visit. *The inclusion and exclusion criteria have been carefully selected to enroll the most appropriate study population while also ensuring the generalizability of the findings.* All participants will engage in a 6-month randomized adaptive intervention and will be followed for an additional six months following the intervention period. The total study duration will be 12 months.

Potential participants will be recruited primarily from partnering HIV specialty clinics in NYC and Birmingham. Persons living with HIV (PLWH) will be included if they meet the following eligibility criteria:

There are limited inclusion criteria to support the generalizability of our findings.

Participants. *Inclusion criteria:*

1) Able to speak, read, and write in English or Spanish;
2) Aged $\geq$18 years;
3) Willing to participate in any assigned arm of the intervention;
4) Having been diagnosed with HIV $\geq$6 months ago;
5) Have an HIV-1 RNA level >200 copies/mL, or at least one “no-show” visit in the past 12 months, or report either not being virally suppressed in the past 12 months or being virally unsuppressed in the past 12 months;
6) Own a smartphone; and
7) Ability and willingness to provide informed consent for study participation and consent for access to medical records.

Participants are not eligible if they meet any exclusion criteria:

1) Reside in a nursing home, prison, and/or receiving in-patient psychiatric care at time of enrollment;
2) Terminal illness with life expectancy <6 months;
3) Planning to move out of the area in the next 12 months.

Our study participants will be recruited from two geographic locations: Birmingham, Alabama and NYC. Electronic medical record (EMR) data from the UAB 1917 Clinic, a Ryan-White funded, patient-centered HIV primary and specialty medical clinic. suggests that at least 1,150 PLWH receiving care at this site during 2018 would meet study inclusion criteria based on viral load results. In NYC, the Comprehensive Health Program of New York-Presbyterian/Columbia (NYP-CHP) is a Ryan White funded, bilingual, patient-centered clinic that emphasizes sexual health, hepatitis management, and HIV care. It primarily serves Upper Manhattan and the South Bronx where residents are disproportionately affected by HIV. NYP-CHP’s large multidisciplinary team

provides HIV care to a population of more than 2,300 children, adolescents, and adults through more than 16,000 visits per year. NYP-CHP clients are 58% male, 40% female, and 2% male to female transgender. We estimate that at least 1,200 PLWH receiving care at the NYC site would meet our inclusion criteria and would be eligible for enrollment.
If we have trouble recruiting, we have access to additional community sites in both NYC and Birmingham as well as entities associated with our academic medical centers with similar demographics. In addition, all members of the investigative team are involved in their institutions' respective and local Centers for AIDS Research (CFARs), which can be utilized to assist with study recruitment via patient registries. Each member of the investigative team is well known in their respective communities.

Study Procedures, Materials, and Potential Risks

Study Procedures and Materials:

All materials for the proposed study obtained from the participants will be in the form of specimens, EMR information, and data. Each Multiple Principal Investigator (MPI), Dr. Rebecca Schnall at CUIMC and Dr. Scott Batey at UAB, will be responsible for ensuring all information is collected according to the study protocol. Information used to identify potentially eligible participants will be obtained using the UAB 1917 Clinic and the NYP-CHP EMR systems. We will also use patient-reported data obtained after consent. Trained and certified professional staff will obtain all data according to detailed study protocols. Data will be collected directly from study participants and their respective EMR and used specifically for research purposes.

The following human subjects-related data elements will be collected for this study with the source(s) of information noted:

- Participant demographic and clinical characteristics including age, sex, gender, race/ethnicity, employment status, and ART adherence (self-report)
- Clinical diagnoses, clinical HIV lab values (CD4 and viral load), medication history, comorbid health conditions, and primary care visit data (electronic medical records)
- Laboratory measured values of CD4 and viral load (study-specific blood draw)
- Notes from the Community Health Worker encounters with the study participants
- Usage data captured through the WiseApp and the electronic pill bottles (CleverCap)

Our study team is extremely prudent in keeping subject data secure and confidential. All laboratory specimens, evaluation forms, reports, and other records will be identified by a unique coded number to maintain participant confidentiality. The material, records, and data obtained through participation in the study will be specific for research purposes. Existing health records may be used with the permission of the participants. Materials will be obtained by trained staff at each study site. Data will be stored using REDCap (Research Electronic Data Capture) at each respective performance site, and, then, the completely deidentified data will be merged at CUIMC. All laboratory specimens will be identified *only* by the identification number. The code linking the participant identification number to subject identifying information (name, address, etc.) is maintained at the study sites through REDCap, and only authorized site personnel have access to the code. Limited individually identifiable private information is collected that is essential for processing participant payments and for analysis purposes.

Potential Risks:

There is no more than a **minimal risk** associated with any of the proposed study activities. The study activities meet the general definition found in Subpart A (46.102) that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological assessments or tests.

The risks of participating in this study are few. Potential risks are those related to venipuncture, discomfort with study interview questions, and potential breaches of confidentiality. It is possible that certain questions on the survey may make participants feel uncomfortable, but participants are free to decline to answer any questions. Additionally, clinical study sites have co-located mental health and/or counseling services that may be consulted should a participant enter crisis. Participation in research can involve loss of privacy. All study data will be maintained on CUIMC, UAB, and BAO servers that are secure and HIPAA compliant. All signed consent forms, study data, and payment receipts used in this study will be kept in locked files at both sites which only the investigators can access. We will also receive a Federal Certificate of Confidentiality which will protect against attempts by law enforcement or other government agencies to access our data.

Venipuncture:
There is a small risk of local hematoma or infection associated with blood sampling. On rare occasions, drawing blood can cause dizziness, presyncope, and even syncope.

Confidentiality and Privacy:
The use of questionnaires, interviews, and collection of personal medical information poses a risk to confidentiality and privacy and may cause embarrassment.

Adequacy of Protection Against Risks
Informed Consent and Assent:
Recruitment for participation in the study will occur following IRB approval. Recruitment strategies will be developed in collaboration with local clinics and community-based organizations (see Recruitment and Retention Plan). Study staff at both sites will complete an in-person training to standardize the recruitment and consenting procedures. The consenting process is part of the initial study visit, which will take place in a quiet meeting room. Volunteers may request a copy of the consent form in advance, and they will be given one at the start of the orientation; time is allowed for review of the consent form. Volunteers then meet with a member of the research team to a) have the study explained in detail; b) discuss their reasons and motivation for wanting to participate to determine whether they are realistic; c) discuss any practical problems (e.g., scheduling conflicts, vacations) that could interfere with participation; d) have their questions answered; and e) demonstrate their ability to provide informed consent by describing their understanding of the major study goals and what is expected of them if they choose to participate.

Participants are given a signed copy of the consent form and a signed copy is maintained in the study chart for each participant. HIPAA authorization is included in the consent form. Each MPI (Dr. Schnall and Dr. Batey) will have the responsibility of ensuring that research personnel are prepared to convey information to participants specific to the study protocol. The individual is informed of the purpose of the study, potential medical and social risks of participation, their right to withdraw at any time, and compensation. If willing to participate, the volunteer and a study team member will sign the document.

Protections Against Risk:
The inclusion/exclusion criteria are designed to assure that participants at highest risk for adverse events (AEs) are excluded while preserving study generalizability. In addition, the specific measures to decrease risks on the study procedures are detailed below.

Venipuncture:
The risks of hematoma and infection are minimized by having trained clinical personnel perform the procedures using sterile techniques.

Confidentiality and Privacy:
Risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting interviews and collection of personal information in a private setting. Reminder text messages will make no mention of HIV. All data will be collected using unique patient identification codes. All laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number to maintain participant confidentiality. All records will be stored in a locked file cabinet. Study data from all sites will be collected and managed using REDCap. REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g., for data types and range checks), audit trails, and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap also includes a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry. Lastly, clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or the National Institutes of Health (NIH).

Unexpected and Serious Adverse Event Reporting:

A detailed monitoring plan will be included as part of the study protocol, submitted to the IRB, and reviewed and approved by the funding Institute and Center before the study begins. Prior to initiation of the study, agreement about the data safety monitoring plan will be confirmed to ensure the safety of subjects and the validity and integrity of the data. The research coordinator at each site will report serious adverse events (SAEs) that are unexpected and study-related immediately to a study physician who will convey this information to the study team, IRB, and NIH. All AEs and SAEs will be captured, reports will be completed, and information will be entered into the study database. A safety report will detail all serious and unexpected AEs or other unanticipated problems that involve risk to study participants or others and whether these appeared to be related to the study-based interventions or research assessment protocols. If the study team, CUIMC or UAB IRB, or NIH has concerns regarding SAEs, the Western IRB will be notified and a copy of the safety summary will be filed with both IRBs. Actions taken by the Western, CUIMC, or UAB IRB offices in response to AE concerns will be reported to the NIH. All AEs will be reviewed every six months, or sooner, with the designated safety officer.

Vulnerable Subjects:
Economically and/or educationally disadvantaged persons will be enrolled. While this group is considered a vulnerable population, the study team has considerable experience enrolling these participants. As these groups carry the burden of the majority of HIV incidence in both study sites and demonstrate considerable challenges with achieving optimal HIV health outcomes, it is important that they are not excluded from participation in this study. Additionally, our study will analyze the potential impact of the intervention(s) on racial and ethnic groups, perhaps providing new information on the disproportionate impact of HIV felt by these populations.

The study will be conducted according to Good Clinical Practice (GCP) guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 CFR (Part 50 – Protection of Human Subjects and Part 56 – Institutional Review Boards) and the Declaration of Helsinki. This protocol will be submitted to the IRB at the Western IRB for approval and will be reliantly reviewed at UAB. The informed consent of each subject will be obtained in accordance with 21 CFR Part 50 and the Declaration of Helsinki before protocol-specified procedures are carried out.

A study research assistant will obtain the participant's written informed consent prior to any study-related procedures. Consent will be documented by the dated signature of the subject. The signature confirms that the consent is based on information that has been understood. Each subject's signed informed consent form will be kept in secure files by the investigators for possible inspection by regulatory authorities.

Potential Benefits of Proposed Research to the Participant and Others

The potential benefits to an individual participant in the study are not known. The potential benefits of the study to others could be considerable. If our hypotheses are true, this study will make a significant contribution towards helping PLWH who are virally unsuppressed improve adherence to their antiretroviral therapy (ART) regimen and ultimately achieve viral suppression. If the intervention is effective, the direct benefit to participants is the increased ART adherence, retention in HIV primary care, and viral suppression. Increasing ART adherence for PLWH will yield significant benefits in current efforts to achieve HIV elimination. Possible risks (i.e., discomfort answering questions, potential confidentiality breaches) are outweighed by the new knowledge gained regarding increasing ART adherence among PLWH.

Importance of Knowledge to be Gained

The knowledge gained from this research will enable the scientific community, clinicians, and PLWH to improve the HIV care continuum in the US. Consistent with the priorities of RFA-NR-20-002, findings from this study will focus on the efficacy of an adaptive Community Health Worker intervention to improve HIV care among PLWH.

Data and Safety Monitoring Plan
Data and Safety Monitoring Plan is attached separately.

ClinicalTrials.gov Requirements
This trial will be registered with ClinicalTrials.gov.

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