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

Rebecca Schnall, PhD, MPH, BSN, FAAN, FACMI

NCT05938413

Protocol Version 03/22/2024

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, leading to poor health outcomes.[6] In response, the US government prioritized 55 areas with a substantial burden of HIV in the Ending the HIV Epidemic (EHE) plan.[7] These suboptimal HIV health outcomes occur at a time when clinicians have limited time and the US healthcare system remains fragmented,[8] further exacerbating the challenges inherent in the lives of underserved, marginalized groups, such as PLWH.[9] Therefore, the development and evaluation of interventions using a cadre of community health workers (CHW) holds promise for addressing these challenges in the US.[10, 11] 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.[12-17] 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.[18, 19] 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.[20-22] 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.[23-25] Therefore, developing effective interventions to enhance ART adherence is essential.

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[26-28] 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.[29] In another domestic study of an online CHW social support ART adherence intervention, substance using participants reported significantly higher overall ART adherence.[30] 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.[31] 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.[32-34] 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,[35, 36] e.g., HIV-related stigma, quality of life, psychosocial distress/stress, adherence medication and skills, and adherence self-efficacy. Prior work 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.[37] In our BA2C RCT, CHW delivered an intervention adapted from ARTAS, a CDC evidence-based intervention (EBI) show 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[38, 39] 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 CleverCap App.

The ubiquitous nature of mHealth technologies in daily life creates opportunities for health behavior management tools that were not previously possible[40] 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,[41, 42] which is particularly relevant to PLWH since a majority represent underserved and minority groups.[43-45] mHealth technology is especially important in the context of improving ART adherence in PLWH.[46] There is preliminary evidence that mHealth technology is a feasible, attractive, accessible, and effective platform for improving ART adherence in PLWH.[47-49] Eighty-one percent (81%) of Americans are smartphone

owners,[50] and there is evidence that underserved populations use smartphones as their primary method for accessing the Internet.[51, 52] Finally, there is evidence that mHealth technology can promote the prevention and management of chronic illnesses such as HIV,[53] thereby allaying weaknesses of the BA2C intervention.

The proposed study will pilot test a remotely delivered intervention, ***C****ommunity* ***H****ealth Worker* ***A****nd* ***M****Health to Im****P****rove Viral* ***S****uppression (****CHAMPS Pilot****)*, in 40 PLWH in the US.

Aim 1. To assess the feasibility of the CHAMPS Remote Intervention.

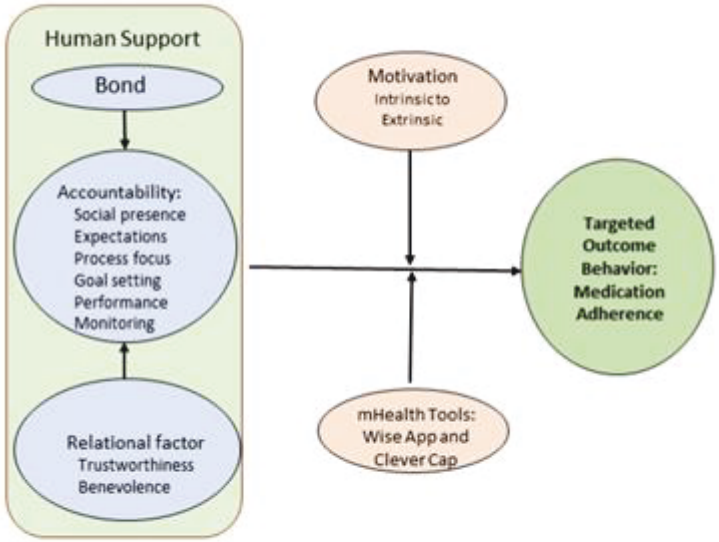
Aim 2. Conduct follow-up interviews to assess the barriers and facilitators to the recruitment, enrollment and retention procedures and to understand the acceptability of the intervention.

This study seeks to expand and strengthen a CHW model through an extant mHealth approach. The pilot study also seeks to establish the feasibility of administering this intervention remotely. Findings will inform the effect of *CHAMPS Pilot* on outcomes related to the HIV Care Continuum in EHE priority settings.

Theoretical Framework

The intervention is guided by the conceptual model of supportive accountability illustrated in **Figure 1**.[54] The model is based on the premise that human support increases medication adherence through accountability to a coach (in *CHAMPS Pilot*– a CHW) who is perceived as trustworthy, knowledgeable, and benevolent.

Figure 1. Model of Supportive Accountability



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.[55-57] 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 Pilot*, are also predictive.[55] Both BA2C and WiseApp—and the proposed integrated intervention, *CHAMPS Pilot*—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.[58-61]

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

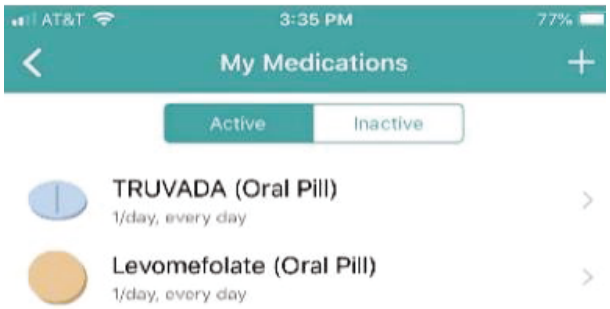
1) **Birmingham Access to Care (BA2C).** BA2C (funded by AIDS United, Co-Is: Batey and Mugavero) was a single-site RCT conducted between July 2013 and February 2016 in partnership with Birmingham AIDS Outreach (BAO) and the University of Alabama at Birmingham (UAB) 1917 HIV Clinic. The study focused 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.[62-64] 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 Pilot* 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[65] 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.[66] 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[67] 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. To assess the feasibility of the CHAMPS Remote Intervention.

Design Overview

A pilot study will be conducted with 40 PLWH over 3 months. Participants will be randomly assigned to CHAMPS Pilot (intervention) or a standard-of-care control arm.

Intervention Arm: The CHAMPS Pilot intervention, outlined in Table 1, is a 3-month intervention guided by BA2C.[62] The CHW will be demographically-matched to our study participant.

Table 1. Components of CHAMPS Pilot delivered over the 3-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,[62] HIV and substance

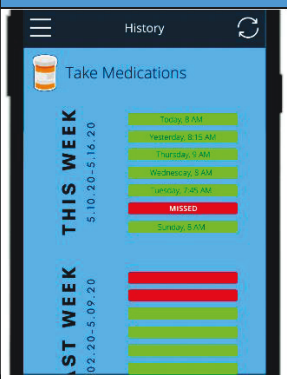
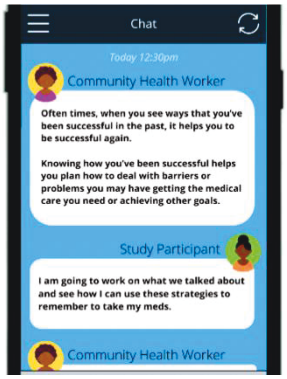
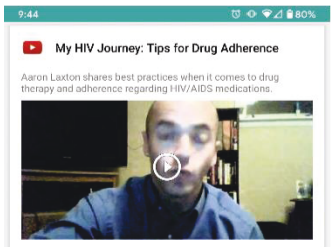
use, and safety in the field. The CHW will also be trained on use of the WiseApp and CleverCap assuring all study participants and CHW are able to successfully use the mHealth technology. Training for the CHW will also be provided on: human subjects research protection, financial conflict of interest, 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 3-month period) will help participants access primary medical care by acknowledging and addressing barriers to care. Participants will participate in CHW sessions via the App. This will help participants overcome many of the challenges to participating in-person, which has been a frequent barrier due to COVID-19.

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 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 Pilot 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.

The remaining visits will be completed remotely through the app. 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 after. The WiseApp has a communication feature which will allow the CHW to deliver all of the sessions described in Table 3 remotely.

Table 2. WiseApp Features used for CHAMPS Pilot 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.	

Standard of Care (Control Arm)

The control condition includes standard health services (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 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.[68] Participants are also provided with mental health and psychosocial support services.

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 Pilot*
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 remotely 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

Eligibility Criteria for Participants

Inclusion criteria:1) Able to speak, read, and write in English or Spanish, 2) Aged ≥18 years; 3) Willing to provide a valid form of identification for verification; 4) Willing to participate in any assigned arm of the intervention; 5) Having been diagnosed with HIV ≥6 months ago; 6) Have an HIV-1 RNA level >50 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; 7) Own a smartphone; 8) Ability and willingness to provide informed consent for study participation and consent for access to medical records; and 9) Live in the United States.

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 <3 months; and 3) Planning to move out of the country in the next 3 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, providing an ART-initiation intervention for these individuals that could compromise our study results.

Recruitment Plan

We will enroll a minimum of 25% women or transgender women and stop enrollment of men at 30 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.[69-73] Participants will be recruited website postings, including Craigslist, Facebook, Instagram, Grindr, Jack'd, and Poz.

Email: If interested volunteers send an email to the study email inbox inquiring about the study, the study staff will re-direct them by providing them the office number so they can call and speak with the study team to get more information about the study.

Consistent with the multi-pronged recruitment approach designed to reduce recruitment bias[74, 75] 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.[76] Dr. Schnall has successfully recruited many African-American, Latino, and female PLWH.[77-80] We plan to enroll a minimum of 50% African-American, Hispanic, Asian, and 25% 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).

STATISTICAL PROCEDURES

Sample Size and Power Calculation

Since this is a pilot study, we will be collecting a sample size to estimate the effect size for future efficacy trials and to establish the feasibility of this intervention.

Sampling approach to successfully enroll PLWH who are not optimally engaged in HIV Care: Using active and passive recruitment methods, the project coordinator will oversee and participate in recruitment efforts. The study staff hired through this project and the peer-to-peer networking efforts will be used to recruit study participants. Our study team 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. Screening will be conducted over the phone 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 DBS (dried blood spot) collection as part of a screening visit. Participants may also sign a Release of Information (ROI) form to allow study staff to access their electronic medical record (EMR) and determine eligibility based on past viral load data and "no-show" visits. Forms completed electronically will be conducted via video conferencing such as Skype, Zoom, or 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 the potential 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.[81-84] Randomization to *CHAMPS Pilot 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 PI Schnall. Following completion of the informed consent and baseline assessment, participants will be randomly assigned to one of two trial arms in REDCap.

Procedures

All study visits will occur remotely via Zoom. Staff members will collect digital 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 study and compensation for time.

Participants in both the intervention and control arms will complete remote visits at the baseline and 3-month follow-up. Following the completion of the baseline study instruments, study participants in the CHAMPS Pilot intervention arm will be mailed 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 remotely throughout the course of the study. Participants will also be provided the opportunity to complete a follow-up interview at their follow-up visit. Follow-up interviews will be recorded via Zoom and will be semi-structured. Study staff members will take field notes and interview recordings will be transcribed prior to analysis.

Dried Blood Spot (DBS) kits will be used to measure participant viral load. DBS kits will be shipped to participants, allowing them to collect their sample in their home or other secure environment. Instructions will be included with the kit, including information about how to collect the dried blood spot and how to mail the sample back to the research team. Participants will be instructed to call research staff to confirm they have

received the kit, have collected the sample, and have mailed the sample back, as well as if they have any questions.

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 and $50 at 3-months as a token of appreciation for their time participating in the study visits and for their dried blood spot samples. Participants electing to complete follow-up qualitative interviews will receive an additional $35.

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.[85]

Data Management

Data will be electronically collected, managed, and secured using REDCap™ by study staff trained on REDCap data entry, management, and security.[86] Quality assurance measures, including built-in skip patterns, validation ranges, and logic checks, minimize data collection and data capturing errors. Quality control measure, including internal monitoring systems and daily and weekly reporting, are run to ensure expedient error correction and to optimize data integrity.

Table 4. Measures and Schedule of Events

	Screening	Baseline	3 mos
Sociodemographic:(e.g., age, race/ethnicity, education, housing)		X	
Primary Outcome Measures			
Viral Load through dried blood spot kit	X		X
Secondary Outcome Measures			
ART adherence (SRSI)[89] and the CleverCap (intervention group only)	X		X
Additional Outcome Measures		X	X
Quality of Life (PROMIS-29)[90]		X	X
HIV Symptom Index[91]		X	X
Engagement in HIV Care[92]		X	X
Mediators			
The HIV Medication Taking Self-Efficacy Scale		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[93]		X	X
Self-regulation skills, which include self-monitoring, goal-setting, and enlistment of self-incentives/plans[94]		X	X
HIV-regulated Stigma[95]		X	X
Moderators			
Alcohol, Smoking & Substance Involvement Screening Test (ASSIST)[83]		X	X
Depression and Anxiety (Beck Symptom Inventory)[96-99]		X	X

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 ≤50 at 3 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,[87, 88] PLWH who take ART as prescribed and achieve and maintain viral suppression have effectively no risk of sexually transmitting the virus to a serodiscordant partner.[87] Our secondary and related outcomes include ART adherence measured in two ways: 1) a single-item self-report measure, an empirically validated instrument,[89] 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.

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.[100] Motivation and outcome expectancies of ART adherence are assessed as three separate dimensions: attitudes, norms, and behavioral intentions to adhere to ART medication.[93] Self-regulation skills, which include self-monitoring, goal-setting, and enlistment of self-incentives/plans, are also assessed.[94] In prior studies of ART adherence, HIV-related stigma and discrimination have been strongly associated with non-adherence;[62,101] 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).[102] 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, and an instrument which was validated by Dr. Schnall for use with PLWH.[90] HIV symptoms and management will be measured with the HIV Symptom Index[91] and Engagement in HIV Care[92] will also recorded at all assessment points.

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 3-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 Pilot 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)[89] 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.[103, 104]

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.[105] 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, 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.[106] A similar GLMM will be used to test sustainability of the intervention at month 3. For this analysis, we will conduct a non-inferiority test[107] to compare viral suppression rate between month 3 and baseline. For primary hypothesis 2 (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.[105] We will also aggregate the electronic pill bottle data at different time points (0 and 3 months) and examine the association between the election pill bottle data and ART adherence data measured by SRSI using Spearman nonparametric correlation.[89] Similar GLMMs or LMMs will be used for secondary outcomes, with GLMMs for binary outcomes and LMMs for continuous outcomes.

Aim 2. Conduct follow-up interviews to assess the barriers and facilitators to the recruitment, enrollment and retention procedures and to understand the acceptability of the intervention.

Data Analysis

Qualitative Data Analysis of Interview Data

The study team will meet and review transcripts and notes from the interviews. Dr. Schnall has 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 Pilot*, 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) is committed to safeguarding the rights and welfare of human subjects in all research activities, and has 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 the Columbia University Institutional Review Board. 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*=40) with HIV infection who are virally unsuppressed in the United States. 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 remote 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 3-month randomized adaptive intervention. The total study duration will be 3 months. A maximum of 25 follow-up interviews will be conducted, with an oversampling of participants in the intervention group.

Potential participants will be recruited online using social media platforms. Persons living with HIV (PLWH) will be included if they meet the following eligibility criteria:

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

Participants. *Inclusion criteria:*

1) Able to speak, read, and write in English or Spanish;
2) Aged ≥18 years;
3) Willing to provide a valid form of identification for verification;
4) Willing to participate in any assigned arm of the intervention;
5) Having been diagnosed with HIV ≥6 months ago;
6) Have an HIV-1 RNA level >50 copies/mL, or report either not being virally suppressed in the past 12 months or being virally unsuppressed in the past 12 months;
7) Own a smartphone;
8) Ability and willingness to provide informed consent for study participation and consent for access to medical records; and
9) Live in the United States

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 <3 months;
3) Planning to move out of the country in the next 3 months.

Our study participants will be recruited nationally.

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. Principal Investigator (PI), Dr. Rebecca Schnall, 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 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 (viral load), medication history, comorbid health conditions, and primary care visit data (electronic medical records)
- Laboratory measured values of viral load (dried blood spot collection)
- Notes from the CHW 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. Data will be stored using REDCap (Research Electronic Data Capture). 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 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 dried blood spot collection, 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, mental health and/or counseling services are available should a participant enter crisis. Participation in research can involve loss of privacy. All study data will be maintained on CUIMC servers that are secure and HIPAA compliant. All signed consent forms, study data, and payment receipts used in this study will be kept in a secured server 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.

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. Study staff will complete a training to standardize the recruitment and consenting procedures. The consenting process is part of the initial study visit, which will take place remotely over Zoom. Volunteers will meet remotely 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 toparticipate.
Participants are provided with a digital 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. The PI, Dr. Schnall, 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.

Confidentiality and Privacy:
Risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting remote 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 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:
The study team will regularly review the data to ensure the integrity and safety of the participants. The research coordinator 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, IRB, or NIH has concerns regarding SAEs, a copy of the safety summary will be filed with the IRB. Actions taken by CUIMC 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 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 for approval. 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 member will obtain the participant's digital 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
The study team will regularly review the data to ensure the integrity and safety of the participants.

References

1. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009;23(11):1397-404. doi: 10.1097/QAD.0b013e32832b7dca. PubMed PMID: 19381076.
2. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaudo H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR, Team HS. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493-505. Epub 2011/07/20. doi: 10.1056/NEJMoa1105243. PubMed PMID: 21767103; PMCID: PMC3200068.
3. Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, Shannon K, Harrigan PR, Hogg RS, Daly P, Kendall P. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet. 2010;376(9740):532-9. doi: 10.1016/S0140-6736(10)60936-1. PubMed PMID: 20638713; PMCID: PMC2996043.
4. Parienti J-J D-DM, Massari V, Guzman D, Deeks SG, Verdon R, Bangsberg DR. Not All Missed Doses Are the Same: Sustained NNRTI Treatment Interruptions Predict HIV Rebound at Low-to- Moderate Adherence Levels. PLoS One. 2008;3(7):e2783. doi: 10.1371/journal.pone.0002783.
5. Prevention CfDCa. Basic Statistics: Centers for Disease Control and Prevention; 2020. Available from: https://www.cdc.gov/hiv/basics/statistics.html.
6. Hygeine NYCDoHaM. HIV Surveillance Annual Report, 2018 November 2019. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/dires/hiv-surveillance-annualreport-2018.pdf.
7. Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. Ending the HIV Epidemic: A Plan for the United States. JAMA. 2019;321(9):844-5. doi: 10.1001/jama.2019.1343.
8. McCarthy M. Fragmented US health-care system needs major reform. The Lancet. 2001;357(9258):782.
9. Kay ES, Rice WS, Crockett KB, Atkins GC, Batey DS, Turan B. Experienced HIV-Related Stigma in Health Care and Community Settings: Mediated Associations With Psychosocial and Health Outcomes. J Acquir Immune Defic Syndr. 2018;77(3):257-63. Epub 2017/11/16. doi: 10.1097/qai.0000000000001590. PubMed PMID: 29140873; PMCID: PMC5807196.
10. Lefeuvre D, Dieng M, Lamara F, Raguin G, Michon C. [Community health workers in HIV/AIDS care]. Sante Publique. 2014;26(6):879-88. Epub 2015/01/30. PubMed PMID: 25629682.
11. Nyblade L, Stangl A, Weiss E, Ashburn K. Combating HIV stigma in health care settings: what works? J Int AIDS Soc. 2009;12:15. Epub 2009/08/08. doi: 10.1186/1758-2652-12-15. PubMed PMID: 19660113; PMCID: PMC2731724.
12. Nachega JB, Adetokunboh O, Uthman OA, Knowlton AW, Altice FL, Schechter M, Galarraga O, Geng E, Peltzer K, Chang LW, Van Cutsem G, Jaffar SS, Ford N, Mellins CA, Remien RH, Mills EJ. Community-Based Interventions to Improve and Sustain Antiretroviral Therapy Adherence, Retention in HIV Care and Clinical Outcomes in Low- and Middle-Income Countries for Achieving the UNAIDS 90-90-90 Targets. Curr HIV/AIDS Rep. 2016;13(5):241-55. Epub 2016/08/01. doi: 10.1007/s11904-016-0325-9. PubMed PMID: 27475643; PMCID: PMC5357578.
13. Levi J, Raymond A, Pozniak A, Vernazza P, Kohler P, Hill A. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. BMJ Glob Health. 2016;1(2):e000010. Epub 2017/06/08. doi: 10.1136/bmjgh-2015-000010. PubMed PMID: 28588933; PMCID: PMC5321333.
14. Levi J, Pozniak A, Heath K, Hill A. The impact of HIV prevalence, conflict, corruption, and GDP/capita on treatment cascades: data from 137 countries. J Virus Erad. 2018;4(2):80-90. Epub 2018/04/24. PubMed PMID: 29682299; PMCID: PMC5892682.
15. Wise JM, Ott C, Azuero A, Lanzi RG, Davies S, Gardner A, Vance DE, Kempf MC. Barriers to HIV Testing: Patient and Provider Perspectives in the Deep South. AIDS Behav. 2019;23(4):1062-72. Epub 2019/01/05. doi: 10.1007/s10461-018-02385-5. PubMed PMID: 30607759; PMCID: PMC6459728.
16. Steehler K, Siegler AJ. Bringing HIV Self-Testing to Scale in the United States: a Review of Challenges, Potential Solutions, and Future Opportunities. J Clin Microbiol. 2019;57(11). Epub 2019/08/30. doi: 10.1128/JCM.00257-19. PubMed PMID: 31462549; PMCID: PMC6813024.
17. Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90-90-90 targets to end the AIDS epidemic by 2020 are not realistic: comment on "Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades". BMJ Glob Health. 2017;2(2):e000227. Epub 2017/06/08. doi: 10.1136/bmjgh-2016-000227. PubMed PMID: 28589026; PMCID: PMC5435269.
18. Mugavero MJ, Lin HY, Allison JJ, Willig JH, Chang PW, Marler M, Raper JL, Schumacher JE, Pisu M,

Saag MS. Failure to establish HIV care: characterizing the "no show" phenomenon. Clin Infect Dis. 2007;45(1):127-30. Epub 2007/06/08. doi: 10.1086/518587. PubMed PMID: 17554713.
19. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, Wilson K, Buchan I, Gill CJ, Cooper C. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med. 2006;3(11):e438. Epub 2006/11/24. doi: 10.1371/journal.pmed.0030438. PubMed PMID: 17121449; PMCID: PMC1637123.
20. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10(9) cells/L. Ann Intern Med. 2003;139(10):810-6. Epub 2003/11/19. doi: 10.7326/0003-4819-139-10-200311180-00008. PubMed PMID: 14623618.
21. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. Clin Infect Dis. 2002;34(8):1115-21. Epub 2002/03/27. doi: 10.1086/339074. PubMed PMID: 11915001.
22. McNabb J, Ross JW, Abriola K, Turley C, Nightingale CH, Nicolau DP. Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic. Clin Infect Dis. 2001;33(5):700-5. Epub 2001/08/07. doi: 10.1086/322590. PubMed PMID: 11486292.
23. Bangsberg DR, Acosta EP, Gupta R, Guzman D, Riley ED, Harrigan PR, Parkin N, Deeks SG. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS. 2006;20(2):223-31. Epub 2006/03/03. doi: 10.1097/01.aids.0000199825.34241.49. PubMed PMID: 16511415.
24. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clin Infect Dis. 2003;37(8):1112-8. Epub 2003/10/03. doi: 10.1086/378301. PubMed PMID: 14523777.
25. Wainberg MA, Friedland G. Public health implications of antiretroviral therapy and HIV drug resistance. JAMA. 1998;279(24):1977-83. Epub 1998/06/27. doi: 10.1001/jama.279.24.1977. PubMed PMID: 9643862.
26. Van Tam V, Larsson M, Pharris A, Diedrichs B, Nguyen HP, Nguyen CT, Ho PD, Marrone G, Thorson A. Peer support and improved quality of life among persons living with HIV on antiretroviral treatment: a randomised controlled trial from north-eastern Vietnam. Health Qual Life Outcomes. 2012;10:53. Epub 2012/05/23. doi: 10.1186/1477-7525-10-53. PubMed PMID: 22606977; PMCID: PMC3491019.
27. Peltzer K, Ramlagan S, Jones D, Weiss SM, Fomundam H, Chanetsa L. Efficacy of a lay health worker led group antiretroviral medication adherence training among non-adherent HIV-positive patients in KwaZulu-Natal, South Africa: results from a randomized trial. SAHARA J. 2012;9(4):218-26. Epub 2012/12/14. doi: 10.1080/17290376.2012.745640. PubMed PMID: 23234350.
28. Robbins RN, Mellins CA, Leu CS, Rowe J, Warne P, Abrams EJ, Witte S, Stein DJ, Remien RH. Enhancing Lay Counselor Capacity to Improve Patient Outcomes with Multimedia Technology. AIDS Behav. 2015;19 Suppl 2:163-76. Epub 2015/01/09. doi: 10.1007/s10461-014-0988-4. PubMed PMID: 25566763; PMCID: PMC4537057.
29. Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, Hooton TM. Peer Support and Pager Messaging to Promote Antiretroviral Modifying Therapy in Seattle: A Randomized Controlled Trial. Jaids-Journal of Acquired Immune Deficiency Syndromes. 2009;52(4):465-73. doi: DOI 10.1097/QAI.0b013e3181b9300c. PubMed PMID: WOS:000271721600005.
30. Horvath KJ, Oakes JM, Rosser BRS, Danilenko G, Vezina H, Amico KR, Williams ML, Simoni J. Feasibility, Acceptability and Preliminary Efficacy of an Online Peer-to-Peer Social Support ART Adherence Intervention. Aids and Behavior. 2013;17(6):2031-44. doi: 10.1007/s10461-013-0469-1. PubMed PMID: WOS:000319990900010.
31. Enriquez M, Cheng AL, Banderas J, Farnan R, Chertoff K, Hayes D, Ortego G, Moreno J, Peterson J, McKinsey D. A Peer-Led HIV Medication Adherence Intervention Targeting Adults Linked to Medical Care but without a Suppressed Viral Load. J Int Assoc Provid AIDS Care. 2015;14(5):441-8. Epub 2014/11/22. doi: 10.1177/2325957414558301. PubMed PMID: 25412724; PMCID: PMC5677528.
32. Olaniran A, Smith H, Unkels R, Bar-Zeev S, van den Broek N. Who is a community health worker? - a systematic review of definitions. Glob Health Action. 2017;10(1):1272223. Epub 2017/02/23. doi: 10.1080/16549716.2017.1272223. PubMed PMID: 28222653; PMCID: PMC5328349.
33. Kangovi S, Mitra N, Grande D, Long JA, Asch DA. Evidence-Based Community Health Worker Program Addresses Unmet Social Needs And Generates Positive Return On Investment. Health Affairs. 2020;39(2):207-13. doi: 10.1377/hlthaff.2019.00981.
34. Kim K, Choi JS, Choi E, Nieman CL, Joo JH, Lin FR, Gitlin LN, Han HR. Effects of Community-Based Health Worker Interventions to Improve Chronic Disease Management and Care Among Vulnerable Populations: A Systematic Review. Am J Public Health. 2016;106(4):e3-e28. Epub 2016/02/19. doi:

10.2105/AJPH.2015.302987. PubMed PMID: 26890177; PMCID: PMC4785041.
35. Geldsetzer P, Vaikath M, De Neve JW, Bossert TJ, Sibandze S, Mkhwanazi M, Barnighausen T. Distrusting community health workers with confidential health information: a convergent mixed-methods study in Swaziland. Health Policy Plan. 2017;32(6):882-9. Epub 2017/04/14. doi: 10.1093/heapol/czx036. PubMed PMID: 28407083.
36. Han HR, Kim K, Murphy J, Cudjoe J, Wilson P, Sharps P, Farley JE. Community health worker interventions to promote psychosocial outcomes among people living with HIV-A systematic review. PLoS One. 2018;13(4):e0194928. Epub 2018/04/25. doi: 10.1371/journal.pone.0194928. PubMed PMID: 29689054; PMCID: PMC5915269.
37. Raper JL, Mugavero MJ, Batey DS. Birmingham Access to Care Study (BA2C): University of Alabama at Birmingham; 2016.
38. Jain KM, Holtgrave DR, Maulsby C, Kim JJ, Zulliger R, Massey M, Charles V. Improving access to HIV care: lessons from five US sites: JHU Press; 2016.
39. Kay ES, Batey DS. Birmingham Access to Care: Results of A Randomized Controlled Trial of a Community Health Worker Intervention to Improve Linkage to and Retention in CareIn Prepartion.
40. Estrin D, Sim I. Health care delivery. Open mHealth architecture: an engine for health care innovation. Science. 2010;330(6005):759-60. doi: 10.1126/science.1196187. PubMed PMID: 21051617.
41. Akter S, Ray P. mHealth - an Ultimate Platform to Serve the Unserved. Yearb Med Inform. 2010:94-100. PubMed PMID: 20938579.
42. Klasnja P, Pratt W. Healthcare in the pocket: mapping the space of mobile-phone health interventions. J Biomed Inform. 2012;45(1):184-98. doi: 10.1016/j.jbi.2011.08.017. PubMed PMID: 21925288; PMCID: PMC3272165.
43. Center for Disease Control and Prevention (CDC). HIV Among Latinos 2014 [cited 2014 June 11]. Available from: http://www.cdc.gov/hiv/risk/racialEthnic/hispanicLatinos/facts/index.html.
44. Centers for Disease Control and Prevention (CDC). HIV Among African Americans Atlanta, GA2014. Available from: http://www.cdc.gov/hiv/risk/racialEthnic/aa/facts/.
45. Hall HI, Song R, Rhodes P, Prejean J, An Q, Lee LM, Karon J, Brookmeyer R, Kaplan EH, McKenna MT, Janssen RS, Group HIVIS. Estimation of HIV incidence in the United States. JAMA. 2008;300(5):520-9. doi: 10.1001/jama.300.5.520. PubMed PMID: 18677024; PMCID: PMC2919237.
46. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev. 2012;3:CD009756. doi: 10.1002/14651858.CD009756. PubMed PMID: 22419345.
47. King E, Kinvig K, Steif J, Qiu AQ, Maan EJ, Albert AY, Pick N, Alimenti A, Kestler MH, Money DMJJomIr. Mobile text messaging to improve medication adherence and viral load in a vulnerable Canadian population living with human immunodeficiency virus: a repeated measures study2017;19(6):e190.
48. Perera AI, Thomas MG, Moore JO, Faasse K, Petrie KJ. Effect of a smartphone application incorporating personalized health-related imagery on adherence to antiretroviral therapy: a randomized clinical trial. AIDS Patient Care STDS. 2014;28(11):579-86. Epub 2014/10/08. doi: 10.1089/apc.2014.0156. PubMed PMID: 25290556; PMCID: PMC4216527.
49. Lewis MA, Uhrig JD, Bann CM, Harris JL, Furberg RD, Coomes C, Kuhns LMJHP. Tailored text messaging intervention for HIV adherence: A proof-of-concept study2013;32(3):248.
50. Center PR. Mobile Fact Sheet2019.
51. Duggan M, Rainie L. Cell phone activities 2012. Pew Research Center. 2012.
52. Pollio DE, Batey DS, Bender K, Ferguson K, Thompson S. Technology Use among Emerging Adult Homeless in Two U.S. Cities. Social Work. 2013;58(2):173-5. doi: 10.1093/sw/swt006.
53. Kirk GD, Himelhoch SS, Westergaard RP, Beckwith CG. Using Mobile Health Technology to Improve HIV Care for Persons Living with HIV and Substance Abuse. AIDS research and treatment. 2013;2013:194613. doi: 10.1155/2013/194613. PubMed PMID: 24381751; PMCID: 3870121.
54. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res. 2011;13(1):e30. Epub 2011/03/12. doi: 10.2196/jmir.1602. PubMed PMID: 21393123; PMCID: PMC3221353.
55. Singh N, Berman SM, Swindells S, Justis JC, Mohr JA, Squier C, Wagener MM. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. Clin Infect Dis. 1999;29(4):824-30. Epub 1999/12/10. doi: 10.1086/520443. PubMed PMID: 10589897.
56. Murphy DA, Marelich WD, Hoffman D, Steers WN. Predictors of antiretroviral adherence. AIDS Care. 2004;16(4):471-84. Epub 2004/06/19. doi: 10.1080/09540120410001683402. PubMed PMID: 15203415.
57. Gardenier D, Andrews CM, Thomas DC, Bookhardt-Murray LJ, Fitzpatrick JJ. Social support and adherence: differences among clients in an AIDS day health care program. J Assoc Nurses AIDS Care.

2010;21(1):75-85. Epub 2009/10/13. doi: 10.1016/j.jana.2009.06.007. PubMed PMID: 19819169.
58. Aneshensel C FR. Stress, support, and depression: a longitudinal causal model. J Community Psychol. 1982;10(4):363-76.
59. Gonzalez JS, Penedo FJ, Antoni MH, Duran RE, McPherson-Baker S, Ironson G, Isabel Fernandez M, Klimas NG, Fletcher MA, Schneiderman N. Social support, positive states of mind, and HIV treatment adherence in men and women living with HIV/AIDS. Health Psychol. 2004;23(4):413-8. Epub 2004/07/22. doi: 10.1037/0278-6133.23.4.413. PubMed PMID: 15264978.
60. Simoni JM, Frick PA, Huang B. A longitudinal evaluation of a social support model of medication adherence among HIV-positive men and women on antiretroviral therapy. Health Psychol. 2006;25(1):74-81. Epub 2006/02/02. doi: 10.1037/0278-6133.25.1.74. PubMed PMID: 16448300; PMCID: PMC5096446.
61. Wills TA, Vaughan R. Social support and substance use in early adolescence. J Behav Med. 1989;12(4):321-39. Epub 1989/08/01. doi: 10.1007/bf00844927. PubMed PMID: 2600962.
62. (CDC) CfDCaP. ARTAS: Evidence-Based for Linkage to HIV Care and Retention in HIV Care 2018 2018. Available from: https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/lrc/cdc-hiv-lrc-artas.pdf.
63. Gardner LI, Metsch LR, Anderson-Mahoney P, Loughlin AM, del Rio C, Strathdee S, Sansom SL, Siegal HA, Greenberg AE, Holmberg SD, Antiretroviral T, Access Study Study G. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. AIDS. 2005;19(4):423-31. Epub 2005/03/08. doi: 10.1097/01.aids.0000161772.51900.eb. PubMed PMID: 15750396.
64. Craw JA, Gardner LI, Marks G, Rapp RC, Bosshart J, Duffus WA, Rossman A, Coughlin SL, Gruber D, Safford LA, Overton J, Schmitt K. Brief strengths-based case management promotes entry into HIV medical care: results of the antiretroviral treatment access study-II. J Acquir Immune Defic Syndr. 2008;47(5):597-606. Epub 2008/02/21. doi: 10.1097/QAI.0b013e3181684c51. PubMed PMID: 18285714.
65. Haberer JE, Kahane J, Kigozi I, Emenyonu N, Hunt P, Martin J, Bangsberg DR. Real-time adherence monitoring for HIV antiretroviral therapy. AIDS Behav. 2010;14(6):1340-6. doi: 10.1007/s10461-010-9799-4. PubMed PMID: 20809380; PMCID: PMC2974938.
66. Hevner A. A three cycle view of design science research. Scand J Inform Syst 2007;2.
67. Research NIoN. The NINR strategic plan: Advancing science, improving lives2016.
68. Services. DoHaH. Department of Health and Human Services HIV guidelines 2020 [cited 2020 May 12, 2020]. Available from: https://aidsinfo.nih.gov/guidelines.
69. Erlandson KM, Allshouse AA, Jankowski CM, Duong S, Mawhinney S, Kohrt WM, Campbell TB. Comparison of functional status instruments in HIV-infected adults on effective antiretroviral therapy. HIV Clin Trials. 2012;13(6):324-34. doi: 10.1310/hct1306-324. PubMed PMID: 23195670; PMCID: PMC4379206.
70. Erlandson KM, MaWhinney S, Wilson M, Gross L, McCandless SA, Campbell TB, Kohrt WM, Schwartz R, Brown TT, Jankowski CM. Physical function improvements with moderate or high-intensity exercise among older adults with or without HIV infection. Aids. 2018;32(16):2317-26. doi: 10.1097/QAD.0000000000001984. PubMed PMID: 30134299; PMCID: PMC6170687.
71. Jankowski CM, Gozansky WS, Van Pelt RE, Wolfe P, Schwartz RS, Kohrt WM. Oral dehydroepiandrosterone replacement in older adults: effects on central adiposity, glucose metabolism and blood lipids. Clin Endocrinol (Oxf). 2011;75(4):456-63. Epub 2011/04/28. doi: 10.1111/j.1365-2265.2011.04073.x. PubMed PMID: 21521341; PMCID: PMC3166648.
72. Jankowski CM, Shea K, Barry DW, Linnebur SA, Wolfe P, Kittelson J, Schwartz RS, Kohrt WM. Timing of Ibuprofen Use and Musculoskeletal Adaptations to Exercise Training in Older Adults. Bone Rep. 2015;1:1-8. Epub 2015/02/03. doi: 10.1016/j.bonr.2014.10.003. PubMed PMID: 25642444; PMCID: PMC4310009.
73. Park YM, Keller AC, Runchey SS, Miller BF, Kohrt WM, Van Pelt RE, Kang C, Jankowski CM, Moreau KL. Acute estradiol treatment reduces skeletal muscle protein breakdown markers in early- but not late-postmenopausal women. Steroids. 2019;146:43-9. Epub 2019/04/01. doi: 10.1016/j.steroids.2019.03.008. PubMed PMID: 30928279.
74. Lloyd CE, Johnson MR, Mughal S, Sturt JA, Collins GS, Roy T, Bibi R, Barnett AH. Securing recruitment and obtaining informed consent in minority ethnic groups in the UK. BMC Health Serv Res. 2008;8:68. Epub 2008/04/01. doi: 1472-6963-8-68 [pii] 10.1186/1472-6963-8-68 [doi]. PubMed PMID: 18373876; PMCID: 2311303.
75. Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participant-friendly system. J Natl Cancer Inst. 1995;87(23):1747-59. Epub 1995/12/06. PubMed PMID: 7473831.
76. Adam GP, Di M, Cu-Uvin S, Halladay C, Smith BT, Iyer S, Trikalinos TA. Strategies for improving the lives of US women aged 40 and above living with HIV/AIDS: an evidence map. Syst Rev. 2018;7(1):25. Epub 2018/02/03. doi: 10.1186/s13643-018-0684-y. PubMed PMID: 29391059; PMCID: PMC5796491.
77. Webel AR, Longenecker CT, Gripshover B, Hanson JE, Schmotzer BJ, Salata RA. Age, stress, and

isolation in older adults living with HIV. AIDS Care. 2014;26(5):523-31. Epub 2013/10/15. doi: 10.1080/09540121.2013.845288. PubMed PMID: 24116852; PMCID: PMC3945181.
78. Webel AR, Higgins PA. The relationship between social roles and self-management behavior in women living with HIV/AIDS. Womens Health Issues. 2012;22(1):e27-33. doi: 10.1016/j.whi.2011.05.010. PubMed PMID: 21798762; PMCID: PMC3206212.
79. Webel AR, Cuca Y, Okonsky JG, Asher AK, Kaihura A, Salata RA. The impact of social context on self-management in women living with HIV. Soc Sci Med. 2013;87:147-54. doi: 10.1016/j.socscimed.2013.03.037. PubMed PMID: 23631790; PMCID: PMC3656470.
80. Webel AR. Testing a peer-based symptom management intervention for women living with HIV/AIDS. AIDS Care. 2010;22(9):1029-40. doi: 10.1080/09540120903214389. PubMed PMID: 20146111; PMCID: PMC3131156.
81. Markaryan T, Rosenberger WF. Exact properties of Efron's biased coin randomization procedure. The Annals of Statistics. 2010;38(3):1546-67. doi: 10.1214/09-aos758.
82. Efron B. Forcing a sequential experiment to be balanced. Biometrika. 1971;58(3):403-17. doi: 10.1093/biomet/58.3.403.
83. Antognini AB, Giovagnoli A. A new 'biased coin design' for the sequential allocation of two treatments. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2004;53(4):651-64. doi: 10.1111/j.1467-9876.2004.00436.x.
84. Antognini AB. A theoretical analysis of the power of biased coin designs. Journal of Statistical Planning and Inference. 2008;138(6):1792-8. doi: 10.1016/j.jspi.2007.06.033.
85. Lyles CM, Crepaz N, Herbst JH, Kay LS. Evidence–Based HIV Behavioral Prevention From the Perspective of the CDC's HIV/AIDS Prevention Research Synthesis Team. AIDS Education and Prevention. 2006;18(supp):21-31. doi: 10.1521/aeap.2006.18.supp.21.
86. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009;42(2):377-81. Epub 2008/09/30. doi: 10.1016/j.jbi.2008.08.010. PubMed PMID: 18929686.
87. Mccray E MJ. Dear Colleague: Information from the CDC Division of HIV/AIDS Prevention: Centers for Disease Control and Prevention; 2019. Available from: https://www.cdc.gov/hiv/policies/dear-colleague/dcl/062719.html.
88. The Lancet H. U=U taking off in 2017. Lancet HIV. 2017;4(11):e475. Epub 2017/11/04. doi: 10.1016/S2352-3018(17)30183-2. PubMed PMID: 29096785.
89. Feldman BJ, Fredericksen RJ, Crane PK, Safren SA, Mugavero MJ, Willig JH, Simoni JM, Wilson IB, Saag MS, Kitahata MM, Crane HM. Evaluation of the single-item self-rating adherence scale for use in routine clinical care of people living with HIV. AIDS and behavior. 2013;17(1):307-18. doi: 10.1007/s10461-012-0326-7. PubMed PMID: 23108721.
90. Schnall R, Liu J, Cho H, Hirshfield S, Siegel K, Olender S. A Health-Related Quality-of-Life Measure for Use in Patients with HIV: A Validation Study. AIDS patient care and STDs. 2017;31(2):43-8. Epub 2017/01/04. doi: 10.1089/apc.2016.0252. PubMed PMID: 28051875.
91. Justice AC, Holmes W, Gifford AL, Rabeneck L, Zackin R, Sinclair G, Weissman S, Neidig J, Marcus C, Chesney M, Cohn SE, Wu AW. Development and validation of a self-completed HIV symptom index. Journal of Clinical Epidemiology. 2001;54(12, Supplement 1):S77-S90. doi: https://doi.org/10.1016/S0895-4356(01)00449-8.
92. Bakken S, Holzemer WL, Brown M-A, Powell-Cope GM, Turner JG, Inouye J, Nokes KM, Corless IB. Relationships between perception of engagement with health care provider and demographic characteristics, health status, and adherence to therapeutic regimen in persons with HIV/AIDS. AIDS patient care and STDs. 2000;14(4):189-97.
93. Amico KR, Toro-Alfonso J, Fisher JD. An empirical test of the information, motivation and behavioral skills model of antiretroviral therapy adherence. AIDS Care. 2005;17(6):661-73. Epub 2005/07/23. doi: 10.1080/09540120500038058. PubMed PMID: 16036253.
94. Reynolds NR. The problem of antiretroviral adherence: a self-regulatory model for intervention. AIDS Care. 2003;15(1):117-24. Epub 2003/03/27. doi: 10.1080/0954012021000039815. PubMed PMID: 12655839.
95. Earnshaw VA, Smith LR, Chaudoir SR, Amico KR, Copenhaver MM. HIV stigma mechanisms and well-being among PLWH: a test of the HIV stigma framework. AIDS Behav. 2013;17(5):1785-95. doi: 10.1007/s10461-013-0437-9. PubMed PMID: 23456594; PMCID: PMC3664141.
96. Naar-King S, Templin T, Wright K, Frey M, Parsons JT, Lam P. Psychosocial factors and medication adherence in HIV-positive youth. AIDS Patient Care & STDs. 2006;20(1):44-7.

97. Derogatis LR. BSI brief symptom inventory. Administration, scoring, and procedures manual. 1993.
98. Nugent NR, Brown LK, Belzer M, Harper GW, Nachman S, Naar-King S, Interventions ATNfHA. Youth living with HIV and problem substance use: elevated distress is associated with nonadherence and sexual risk. Journal of the International Association of Physicians in AIDS Care. 2010;9(2):113-5.
99. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clinical psychology review. 1988;8(1):77-100.
100. Erlen JA, Cha ES, Kim KH, Caruthers D, Sereika SM. The HIV Medication Taking Self-efficacy Scale: psychometric evaluation. J Adv Nurs. 2010;66(11):2560-72. Epub 2010/08/21. doi: 10.1111/j.1365-2648.2010.05400.x. PubMed PMID: 20722799; PMCID: PMC2970730.
101. Rao D, Kekwaletswe TC, Hosek S, Martinez J, Rodriguez F. Stigma and social barriers to medication adherence with urban youth living with HIV. AIDS Care. 2007;19(1):28-33. Epub 2006/11/30. doi: 10.1080/09540120600652303. PubMed PMID: 17129855.
102. Humeniuk R AR. Validation of the alcohol, smoking and substance involvement screening test (ASSIST) and pilot brief intervention: a technical report of phase II findings of the WHO ASSIST project. Geneva: World Health Organization. 2006
103. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res. 2011;2(3):109-12. doi: 10.4103/2229-3485.83221. PubMed PMID: 21897887.
104. Fisher LD. Intention to treat in clinical trials. Statistical issues in drug research and development. 1990.
105. Hedeker D GR. Longitudinal Data Analysis. Hoboken, NJ: Wiley-Interscience; 2006.
106. Tang M, Slud EV, Pfeiffer RM. Goodness of Fit Tests for Linear Mixed Models. J Multivar Anal. 2014;130:176-93. Epub 2014/09/01. doi: 10.1016/j.jmva.2014.03.012. PubMed PMID: 28503001; PMCID: PMC5426279.
Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. J Gen Intern Med. 2011;26(2):192-6. Epub 2010/09/21. doi: 10.1007/s11606-010-1513-8. PubMed PMID: 20857339.