SUpporting Sustained HIV Treatment Adherence after INitiation (SUSTAIN)

Study Protocol

Version number: 2.1

Amendment approved 13 July 2022

A collaboration between:

Department of Global Health
Boston University School of Public Health (BUSPH)
Boston, MA, USA

Desmond Tutu Health Foundation
Cape Town, South Africa

Center for Global Health
Massachusetts General Hospital
Boston, MA, USA

New York University,
New York, NY, USA

PART A: General information:

A1. SUpporting Sustained HIV Treatment Adherence after Initiation

Short name: SUSTAIN

A2. Principal Investigator (BU):

Dr. Lora Sabin, MA, PhD
Associate Professor of Global Health
Department of Global Health
Boston University School of Public Health
Email: lsabin@bu.edu

Principal Investigator (UCT):

Dr. Catherine Orrell, MBChB, MSc, MMed, PhD (PI – Cape Town)
Associate Professor
Department of Medicine
University of Cape Town
Email: Catherine.Orrell@hiv-research.org.za

A3. Co-Investigators and collaborators

a) Boston University

Dr. Allen Gifford, MD
Professor of Medicine, Boston University School of Medicine
Professor of Public Health, Boston University School of Public Health
Boston, MA, USA
Email: agifford@bu.edu

Nafisa Halim, PhD, MA
Assistant Professor of Global Health
Department of Global Health
Boston University School of Public Health
Email: nhalim@bu.edu

Dr. William MacLeod, ScD, MS
Associate Professor of Global Health
Department of Global Health
Boston University School of Public Health
Email: wmacleod@bu.edu

b) Desmond Tutu Health Foundation

Dr. Lauren Jennings, MBChB, MSc
Site Investigator
DTHF, Gugulethu Research Offices
Email: lauren.jennings@hiv-research.org.za

Ms Laura Myers
Behavioural Scientist
DTHF (consultant), Gugulethu Research Offices
Email: lauramyers@gmail.com

c) Massachusetts General Hospital
Dr. Jessica E. Haberer, MD, MS
Associate Professor, Harvard University School of Medicine
Center for Global Health, Massachusetts General Hospital
Boston, MA, USA
Email : jhaberer@partners.org

d) New York University
Dr. Marya Gwadz, PhD, MS
Professor of Social Work
Silver School of Social Work, New York University
New York, NY, USA

e) City of Cape Town
Dr. Natacha Berkowitz, MBChB, MPH
Epidemiologist
City of Cape Town, South Africa
Email: Natacha.Berkowitz@capetown.gov.za

A4. Research Assistants
Ms. Rebecca West, DrPH program
Boston University School of Public Health
Email: rlwest@bu.edu

Ms. Jeanette Kaiser
Boston University School of Public Health
Email: jlkaiser@bu.edu

A5. Type of study: Clinical trial
ClinicalTrials.gov number: NCT05040841.

A6. Funding Source: NIH/NIMH
1R01MH125703-01A1

Table of Contents

PART B: Study information

B1. Study summary

In South Africa, only 40-75% of those on treatment achieve viral suppression, both through poor adherence and loss to care. The greatest losses to care occur in the first year on ART, with the bulk occurring within the first four months of treatment. The objectives of this protocol will be delivered using a Multiphase Optimization STrategy (MOST) design to test combinations of five effective and feasible ART adherence monitoring or support components. Our objectives are to improve ART adherence, retention and viral outcomes in people commencing ART in the South African public sector, a low-resource setting, over 24 months. The study team has worked closely with the City of Cape Town (CoCT) Health Management Team over the past three years to identify these five components, which we believe will enable rapid identification and management of poor adherence.

We will implement a 24-month fractional factorial design study (Aim 1). We will recruit 512 patients initiating ART at three CoCT ART clinics. Each will have adherence monitored using the Wisepill® electronic adherence monitoring device (EAM). After eligibility has been confirmed, each participant will be randomized to one of 16 experimental conditions, as indicated in Figure 1 (page 9 below). Each condition includes a unique combination of five adherence intervention components. Three of these components focus on identifying individuals with poor adherence with increasing degrees of sophistication (M1, M2 and M3) with immediate linkage to adherence support. Two components focus on supporting good adherence (S1 and S2). They both supplement the existing adherence support program delivered at CoCT clinics (standard of care component). Based on Self-Determination Theory, we postulate these intervention components will: 1) enhance feelings of autonomy support, social support, and knowledge; 2) improve motivation and self-competence; and 3) increase ART retention, adherence, and viral suppression. A subset of the participants, as well as clinic and study staff, will be invited to in-depth interviews to explore mediating factors (Aim 1) and the implementation process (Aim 2); and the data collected in Aims 1 and 2 will be used to explore cost effectiveness (Aim 3).

B2. Management of information

For close coordination, we will organize regular Zoom or skype calls between the Boston-based researchers and local researchers in Cape Town and New York City to discuss study progress, any study-related issues, and to resolve problems as they arise. During data collection, the Cape Town researchers will be using REDCap to collect and manage data. Dr. Orrell will overview these activities, but if any problems emerge, they will be discussed during our regular calls. Data will be available to the BU-based researchers via the REDCap system. All data will be secured and only available to study personnel.

B3. Nature of relationship with foreign site(s)

This protocol represents the latest step of collaboration with Dr. Catherine Orrell (MPI with Dr. Sabin) at the DTHF. It builds directly on the LEAP project (BUMC IRB #38872), which was a collaboration from 2019-20. With a sub-award from BU, Dr. Orrell will lead the Cape Town team, with primary responsibility for all local research activities, including subject recruitment and follow-up, and data collection and management. As noted above, she will obtain IRB approval directly from two key organizations in Cape Town. The BUSPH collaborators will collaborate with Dr. Orrell on other major elements of the project, including study design, development of protocol and data collection tools, training for data collection,

monitoring of data collection, and report-writing. Data analysis will mainly be conducted at BU (with access to data via the secure REDCap system). Data interpretation and written or presentation products will be done collaboratively by all the investigators.

The protocol will be submitted simultaneously to the IRBs named above.

B4. International Research

Some researchers, namely Dr. Sabin, Dr. Gifford, Dr. Halim, and Dr. MacLeod, may have contact with study participants in Cape Town.

B5. Ethical approvals

We will obtain ethical approval at the Boston University Medical Center and the University of Cape Town (FWA00001637). We will also obtain ethical approval from the City of Cape Town Research Committee per local custom.

B6. Training of local investigators

MPI Dr. Orrell will oversee and be responsible for all in-country activities in South Africa, including training activities of study staff. Study-specific training will encompass: patient recruitment, data collection and management, use of the EAM (electronic adherence monitors), as well as retention monitoring. Training in ethical issues (ensuring confidentiality, the right of subjects to refuse participation, etc.) as well as in procedures to ensure compliance with the approved protocol, will be conducted by Dr. Orrell. She may make use of human subjects training documents used by BMC/BU medical campus investigators if useful.

PART C: Background and rationale

Advances in antiretroviral therapy (ART) have reduced illness and death for people living with HIV (PLWH), but major gaps in the care continuum persist. Sub-Saharan Africa is home to nearly 70% of the world's PLWH; South Africa, with 7.7 million PLWH, bears the continent's greatest HIV burden. By 2018, nearly five million PLWH had accessed ART in South Africa, but weaknesses were clear: 17% of PLWH who start ART fall out of care by 16 weeks; >20% are lost in the first year.[1-3] Adherence in South Africa ranges from 40%-75%.[3-5] Mainly due to poor adherence and retention, only 51–86% show suppressed virus at 12 months;[3,4,6-9] overall, <50% of PLWH are virally suppressed.[10] These outcomes predict higher mortality, more HIV transmission, and drug-resistant HIV, hindering the World Health Organization's "End HIV/AIDS by 2030" goals.[11]

Early detection of poor adherence and linkage to support for new patients is critical. The evidence shows that patients who miss doses early in treatment go on to miss clinic visits, exhibit poor outcomes, and be disproportionately lost to care.[12-19] Data from our proposed study sites show that PLWH with unsuppressed virus (>1000 copies/ml), indicating poor adherence, were more likely to be lost to care in later years than virally suppressed patients.[20,21] The most widely used way to monitor adherence (e.g., self-report) is often unreliable.[2,22,23] Other objective and more timely methods have strengths and weaknesses. *Electronic adherence monitors (EAM)* that track adherence in real time are acceptable and feasible in many settings[24-30] and have been used as reminder tools. New WHO guidelines promote EAM,[31] with relevant research moving apace;[32,33] EAM is also now included in the Global Drug Facility's product catalog.[34] In HIV treatment, the benefit-cost ratio of EAM is unknown. Another method that leverages existing infrastructure is *pharmacy refill monitoring (PRM).* PRM data are associated with viral load (VL),[2,35,36] but can only detect nonadherence after a missed refill. Both EAM and PRM are effective monitoring tools, but data on integrating nonadherence detection with adherence support programs are limited.[37] A third approach is immediate patient outreach when unsuppressed virus is detected. Immediate outreach is not done in most low-resource settings, but is feasible and well-liked by patients.[38] Each of these three methods is included in our study, allowing us to determine which—or what combination—is most effective in identifying nonadherence and improving viral suppression.

Evidence-based strategies exist, but translation into clinical practice has been slow. In Cape Town, translation of research is underway. City of Cape Town (COCT) officials have established Risk of Treatment Failure (ROTF) clinics,[39] where patients with elevated virus (VL >1,000 copies/ml) receive extra support via a) one nurse-led counseling session and b) peer groups (4 sessions). The evidence shows ROTF help, but could be better. Viral re-suppression is 30-70% in those referred to a ROTF clinic.[40] The COCT plans to strengthen ROTF clinics, based on evidence of effect and feasibility. After working with us to assess relevant research and collect pilot data (through the LEAP pilot project, BUMC IRB #38872), COCT officials will consider new modes of nonadherence detection for ROTF clinics and two support elements with clear impact on adherence: enhanced peer group support and weekly check-in text messages. The present study will provide evidence on how best to combine these options and offer a model for improving ART outcomes in other low-resource settings.

We know that sustainable interventions must be affordable and cost-effective. In a world of limited resources, it is critical to consider both the costs and costs relative to effect (cost-effectiveness) of new support programs, including those utilizing new technologies such as EAM. Currently, several EAM options are on the market, ranging from $32-200/device or more, depending on functionalities. We propose to use one made by Wisepill Technologies, which uses cellular signals triggered by openings

sent to a server in South Africa. Each EAM holds a month's supply of ART pills with a rechargeable battery. This device has been used in resource-poor settings, including South Africa, Uganda, and China, to monitor or improve ART adherence. We have chosen this EAM for practical reasons (the size is suitable for ART tablets, the data systems are robust), but the study will generate data on the benefits of EAM generally. Importantly, its cost is expected to drop.

Regarding the EAM device for this study, our study team has considerable experience with use of this device and others like it. The BU team has utilized this specific device (made by Wisepill Technologies[41]) in several studies approved by the BUMC IRB (H-32876 and H-31466) as well as similar devices that have slightly different specifications (H-37384, H-39376, and H-25495). In addition, the local team led by the co-PI, Dr. Orrell, has used this device in several studies approved by the University of Cape Town (FWA00001637), including the META study (funded by the Gates Foundation),[4] TAP study (funded by European and Developing Countries Clinical Trial Partnership),[3] and the ADDART study (NIH R01 - R01-AI122300).

The study's primary research goal is to identify the optimal combination of evidence-based and scalable HIV interventions for low-resource, high-burden settings. We propose to 1) test the relative contribution of five promising intervention components; 2) collect cost and other implementation data; and 3) create a multi-component intervention package to optimize cost-effectiveness and implementation success. Of the five components, three are methods of non-adherence detection plus patient outreach; two are adherence support methods that can be integrated into Cape Town healthcare systems. These will not overcome all challenges that ART patients experience (e.g., structural barriers such as food insecurity) but they represent scalable, feasible, acceptable, and effective options. Notably, they are all behavioral approaches grounded in the experience and priorities of local health officials with whom we have worked to identify scaleable interventions. While the study will be in Cape Town, it is broadly adaptable to other resource-limited settings.

The gold standard for testing interventions is the randomized controlled trial (RCT), which minimizes bias when testing cause and effect of a new exposure. When testing an intervention with more than one element, however, untangling the effect of individual elements is impossible. Indeed, data on the performance of individual components and their interactions—critical for developing and refining the components of a packaged intervention—is lost in an RCT. Notably, clinical care typically relies on packages of services, not single interventions, and packaged interventions are recommended for ART support.[42,43] An effective way to test a multi-component intervention is to use the novel Multiphase Optimization STrategy (MOST), an engineering-inspired method for identifying the most efficacious combination of components in a packaged intervention, thus allowing researchers to drop inactive or weakly-performing components and construct an optimized package based on effect, cost, and other features. Once the optimized multi-component intervention is chosen, an RCT or quasi-experiment can follow to determine whether the optimized package yields superior outcomes compared to existing standards. MOST encompasses three phases: 1) preparation; 2) optimization; and 3) evaluation, often in an RCT. In this project, we have completed preparation, including the pilot LEAP study in Cape Town. SUSTAIN will comprise the middle optimization phase. The evaluation phase will be the focus of a future study.

Our specific aims are:

Aim 1. Employ a highly efficient fractional factorial design to determine the effects of five intervention components on the primary outcome (HIV viral suppression) and secondary outcomes (ART adherence

measured by EAM, ART retention per clinic records, days of unsuppressed virus, time to nonadherence detection, and time to linkage to support). We will explore effect mechanisms quantitatively and qualitatively.

Aim 2. Evaluate the intervention components to address implementation, service, and client outcomes according to the Proctor framework. Data collection will involve tracking of intervention component use, time and motion studies, and quantitative surveys and qualitative interviews with participants and staff.

Aim 3. Use the effectiveness data collected in Aim 1 and the implementation and client outcomes in Aim 2 to model the multi-component intervention optimized for cost-effectiveness and implementation success.

Study Summary

This study is designed to advance the translation of evidence-based interventions into clinical settings to benefit patients. There is ample evidence on what works to support ART adherence and retention—much of it from our own research. We partnered with local officials and clinical staff in Cape Town to review the evidence and to conduct formative research to identify the most effective, acceptable, and feasible intervention options for patients and providers. The proposed study represents the next critical step: we will test the intervention components that emerged from our formative work, encompassing elements to both rapidly identify nonadherent patients and to strengthen the support they receive once identified, to provide the data needed to construct the most cost-effective and sustainable multi-component intervention. Our choice of intervention components will allow a critical test of advanced monitoring technology compared to simpler tools to identify nonadherence. By using an innovative MOST design to guide collection and analysis of efficacy, cost, and other implementation data, the study aligns with NIH's goals of using novel scientific methods to advance implementation science (NOT-OD-15-137). In sum, this project involves cutting edge and urgently needed science relevant to researchers and policy-makers engaged in global HIV.

PART D: Subjects

D1. Inclusion Criteria

Aims 1 and 2, participants in the main trial:

- Adults (≥18 years) and adolescents 16-17 years.
- HIV-positive and attending a local City of Cape Town (COCT) clinic to commence first-line ART, either single tablet regimen, ie tenofovir/lamivudine/dolutegravir (TLD) or tenofovir/emtricitabine/efavirenz (TEE).
- Able to provide full informed consent, with a written signature. For those who are illiterate, a witness will be present throughout the process and will sign the form, while the participant will add their right thumb print. For those who are aged 16-17 years, informed written assent will be obtained, and the adolescent must have a parent or guardian who can provide full informed consent (see **below for how parent/guardian is defined for this purpose).
- Access to a working cellphone and willingness to receive study-releated messaging on that phone.
- Willingness to comply with study procedures, including providing regular updates of contact details /locator information, and use a EAM device for the duration of participation.

In-depth interviews (IDIs) with subset of trial subjects at baseline and months 12 and 24.

- Participation in the main trial.
- Self-reported prior experience with substance use, depression, gender inequity, stigma, or transport/clinic issues.

Aim 2: Questionnaires and IDIs with staff members at study clinics (three total clinics).

- Adults (≥18 years)
- Staff at study clinics, providing HIV care and/or treatment
- Study staff assisting with delivery of interventions

Aim 2: Focus group discussion (FGD) with City of Cape Town officials.

- Adults (≥18 years)
- Staff at City of Cape Town.

** Parent/guardian will be defined per the standard operating procedures of the Desmond Tutu Health Foundation as follows:

- Both parents, if married, are legal guardians
- If child is born out of wedlock, the mother is the natural guardian. If unmarried mother herself is a minor, her mother (i.e. the maternal grandmother) will the child's guardian.
- An unmarried father with proof of paternity (e.g. unabridged birth certificate)
- If parents are deceased, a High Court-appointed adult can act as the guardian.

Confirmation of guardianship will be made as follows:

- Study staff will request proof of identification from the parent(s) and a birth certificate of the child to confirm that the adult is the legal guardian.
- For the father, an unabridged birth certificate may be required to confirm paternity. Additional documentation, eg copy of a marriage certificate, may also be requested.
- In the case of a legal guardian, the staff must request a copy of the court letter assigning guardianship.

D2. Exclusion Criteria

Aims 1 and 2, main trial:

- Clinical conditions as assessed by the COCT clinic clinicians at first visit e.g. renal disease, which preclude the use of a single tablet regimen (with the exception of those on TB treatment who are required to take an extra dose of dolutegravir daily).
- ART is being given in liquid formulation
- Planning to leave Cape Town permanently within the next 24 months.
- Being perinatally infected with HIV. Being infected from birth typically means a set of experiences and complications at a young age that require unique and special attention.
- If an adolescent, taking their ART medication as a syrup, as they are required to use the electronic adherence monitor (Wisepill device), which is only suitable for tablets.

Aim 1: IDIs with trial subjects.

- None.

Aim 2: Questionnaires and IDIs with staff (study and clinic) members at clinics.

- None.

Aim 2: FGD with City of Cape Town officials.

- None.

D3. Subjects: Race/ethnicity

The study is being conducted in Cape Town, South Africa, among people living with HIV on antiretroviral therapy (ART), ART providers in community clinics, and stake-holders at the City of Cape Town. The study population will reflect those populations.

D4. Limited and non-readers

Limited and non-readers will not be excluded from this study.

D5. Vulnerable participants

We will include the following populations designated as vulnerable in recruitment:

- Pregnant women
- Women of child-bearing potential
- Non-English speaking subjects
- Minors

We will protect the rights of members of vulnerable populations, and all study participants, by stressing the voluntary nature of participation, the right to refuse participation without penalty, and provision of informed consent before proceeding with enrollment of participants.

Pregnant women will be included in this study, as they are a group at increased risk, across sub-Saharan Africa, of poor ART outcomes, usually due to poor adherence during pregnancy and poor maintenance of therapy in the early months after delivery. It is essential that adherence in this group is improved, in

order to protect their own life as well as the lives of their current and future babies. Including these women is scientifically appropriate.

The pregnant women and their unborn babies will be at no increased risk through study participation. The study will not impact on the choice of ART made for the pregnant women. Through potentially improving adherence to ART, this research holds the prospect of direct benefit to both the mother and her unborn baby.

Similarly, we are including older adolescents aged 16 and above. These individuals are also at increased risk of poor ART retention and adherence and thus are being included purposefully. During the informed consent and assent process (for both Aims 1 and 2), we will endeavor to be clear about what study participation entails so that these adolescents make an informed decision understanding the risks involved—and with their guardians—make the best choice for themselves.

For non-English speaking participants, we highlight the fact that the study is taking place in South Africa, with local collaborators who are very experienced conducting research in our study population.

More details on recruitment, and procedures to protect vulnerable populations during recruitment, are described in the recruitment section.

PART E: Design/Procedure

E1. Study procedures

This study will be conducted entirely at three City of Cape Town (CoCT) clinics in the Klipfontein Health district of Cape Town. Please note that due to concerns about the SARS-COV-2 epidemic, all routine COVID-related procedures that are locally required will be followed by study staff. Study staff will have been trained in and observe mask-wearing, social distancing, etc. where such protections are being recommended or required. Please see additional information attached as “GRO COVID Plan.”

To achieve Aim 1, we will employ a randomized trial design. We aim to recruit 512 ART-naïve people living with HIV who are eligible to commence ART in these public-sector clinics. Once eligibility is determined, and potential participants provide consent, they will be enrolled. After enrollment, we will dispense a Wisepill device and randomize participants to one of the 16 experimental conditions, which are unique combinations of five intervention components (see Figure 1). They will each participate in the study for a total of 24 months.

Randomisation: Randomization will occur within the study REDCap database, an easy to use and reliable open source system. The study statisticians in Boston will create the randomisation coding for REDCap. The study staff on site in Cape Town who enroll subjects will then access REDCap to complete the assignment.

In essence, numbers between 1 and 512 will be randomly assigned to 16 groups (1 to 16) in advance via excel and assigned by study number in RedCap. Study condition will be assigned sequentially as eligibility is confirmed complete in RedCap.

All assignments will be recorded in clinic folders and in the study REDCap database per procedures used previously by team members; all study staff will be trained to minimize contamination. Participants will

not be able to self-select into a specific intervention.

Figure 1. Intervention components and experimental conditions in the fractional factorial design

Experimental condition Intervention components	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
SoC: After a VL test shows unsuppressed virus, patient is alerted at next clinic visit and given a counseling session	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
M1. Outreach to patient due to unsuppressed VL Test Result (M1/OTR)	O	O	O	O	O	O	O	O	X	X	X	X	X	X	X	X
M2. Pharmacy Refill Monitoring (PRM) + Outreach to the patient (M2/PRM)	O	O	O	O	X	X	X	X	O	O	O	O	X	X	X	X
M3. Electronic Adherence Monitoring (EAM) + Outreach to the patient (M3/EAM)	O	O	X	X	O	O	X	X	O	O	X	X	O	O	X	X
S1. Weekly check-in text messages (S1/Text)	O	X	O	X	O	X	O	X	O	X	O	X	O	X	O	X
S2. Peer group support: Basic (B) or Enhanced (E) (S2/Peer)	E	B	B	E	B	E	E	B	B	E	E	B	E	B	B	E

SoC: standard of care; VL: viral load; M: monitoring method; S: support method.

In addition to the five intervention components, all participants will receive a standard of care support program per existing clinical practice in Cape Town. The only exception is that subjects who are randomized to a condition with the "enhanced peer group support" as opposed to basic peer group support (which means standard of care) will not engage in the latter. In all other randomized conditions, subjects will receive all aspects of standard of care at a minimum, which includes basic peer group support.

Standard of care (SoC) component.

All those on ART in the Western Cape receive additional adherence support as a standard of care once detected as nonadherent (e.g. through indication of unsuppressed HIV virus following a standard viral load test). This takes the form of a risk of treatment failure (ROTF) clinic, that includes an individual structured adherence session with an ART clinician and an invitation to attend 4 x 60-minute peer support group sessions over 4-8 weeks. A VL test is repeated three months after initial ROTF visit. All those identified as having poor adherence during the SUSTAIN study (via either M1, M2 or M3) will receive this care as a minimum.

Intervention components:

These include three monitoring components (finding poor adherence) and are supplemented by two adherence support components (supporting high adherence):

M1/OTR - immediate outreach to patient after a detectable VL:

Standard of care viral loads are drawn at month 4, month 12 and annually thereafter. Those with a raised viral load are often not immediately recalled, but identified at their next visit (1-2 months later) and asked to attend the "Risk of Treatment Failure" (ROTF) clinic for adherence support when they next attend. For participants assigned to M1 we will add a call or other outreach (e.g., text, Whatsapp, in accordance with the outreach methods patients indicate are appropriate for them at the Enrollment visit); to the patient as soon as a raised viral load result is received (±3-5 days), thus expediting entry to existing adherence support. There are two chances to be identified as nonadherent and linked

immediately to existing adherence support in the first 12 months of care with M1.

M2/PRM - immediate outreach after a missed pharmacy refill:

For participants assigned to M2 we will contact the participant if they fail to collect medication from the pharmacy. A participant who is ≥7 days late for a monthly medication pick-up or 14 days late for a 2-monthly pick-up will be notified, again expediting entry to existing adherence support. There are 8-10 chances of being identified as nonadherent and linked immediately to existing adherence support in the first 12 months of care with M2.

M3/EAM - immediate outreach after EAM-identified missed doses:

For participants assigned to M3 we will contact the participant if they miss ≥4 doses or any three consecutive doses in a 14-day period, reviewed weekly. There are 52 chances of being identified as nonadherent and linked immediately to existing adherence support in the first 12 months of care with M2.

S1 - Weekly check-in texts:

Those assigned to S1 will receive weekly check-in texts in addition to the core adherence support component in the event they are identified as nonadherent and are linked with the Risk of Treatment Failure clinics. Participants will be sent weekly simple but supportive text messages e.g. “how are you?” with the offer of a follow-up voice call for 16 consecutive weeks after being identified as nonadherent.

S2 - Enhanced peer group support (E vs B):

Those assigned to S2 will receive an **e**nhanced form of peer group support. Standard of care **B**asic peer groups are led by lay counsellors and provide social support and education; this will continue to be provided to all patients who are not assigned to the enhanced version. “**E**nhanced” peer group support will *replace* the **B**asic standard of care 4 x 60 minute peer groups; and aim to improve long-term maintenance of adherence through motivational interviewing over 4-8 weeks.

Description of patient participant flow and experience of the study:

Depending on randomization assignment to condition 1-16, a participant may be detected as nonadherent by M1, M2, and/or M3. At the first such detection, a participant will immediately receive the SoC component (individual counseling session), plus one or more support component(s) (S1 or S2) as indicated by random assignment.

Once linked to SoC adherence support,participants will receive support for 12-16 weeks. All monitoring components, depending on assignment, will remain active during this time. Participants assigned to a condition with no monitoring components will receive only SoC notice of unsuppressed virus at the next clinic visit after a VL test (month 4 or 12). The last chance to be identified as nonadherent by M1, M2, or M3 will be in month 12; support components (S1, S2) will end by month 15-16. Final assessments will occur at month 24 (see data collection below).

Examples of participant flow through the study.

1. A patient randomized to condition 7 (see Figure 1), for example, will be assigned to M2, M3 and S2-E. This patient will be monitored by EAM and pharmacy refill. Should the patient not miss doses (as per M3) and collect medication on time (as per M2) he/she will not be identified as nonadherent and will progress through the study without intervention. Should the patient miss doses or fail to collect

medication, whichever came first, the patient will be identified as nonadherent and contacted to attend the clinic to be linked to adherence support (the existing ROTF clinic). This support will include the standard of care clinician-based counselling session; but rather than the basic peer group support offered by the clinic, the participant will receive enhanced peer support (S2-E). During the 4-8 weeks of the adherence intervention, adherence will continue to be monitored and any nonadherence noted, but the intervention process will continue until completion (i.e. will not be re-started at each nonadherence detection event). Once the support program is completed, the patient will again be eligible for linkage to the ROTF clinic within the 12 months post-enrollment period. Thus, each patient may undergo the intervention process twice within the first year of the study.

2. A patient randomized to condition 14 (Figure 1), for example, will be assigned to M1, M2, S1 and S2-B. This patient will be monitored by viral load and pharmacy refill. Should the patient collect medication on time (as per M2) and have a suppressed viral load at months 4 and 12, he/she will not be identified as nonadherent and will progress through the study without intervention. Should the patient fail to collect medication or have a raised viral load, whichever came first, the patient will be identified as nonadherent and contacted to attend the clinic to be linked to adherence support. This support will include the standard of care clinician-based counselling, (one counselling session), 16 weeks of weekly text check-ins (S1), and basic peer support (S2-B). During the 16 weeks (given the time needed for the text messages) required to complete this support program, the participant will continue to be monitored and any nonadherence noted, but any additional detection of poor adherence will not reset the adherence intervention, which will continue until completion. Once the support program is completed, the patient will again be eligible for linkage to the ROTF clinic within the 12 months post-enrollment period. Thus, each patient may undergo the intervention process twice within the first year of the study.

Study enrolment by patients will include participation in both quantitative and qualitative data collection at several time points through the 24-month trial (a more detailed description of data collection is described in the “Data collection” section). They will also participate passively in adherence monitoring and tracking of their retention in care (see Data collection).

A schedule of these events for trial participants is provided in Table 1.

A visit will be considered missed if the participant does not attend during the visit window.

Table 1. Schedule of events:

Source:	Procedure:	Screen	Month 0	Month 4	Month 8	Month 12	Month 18	Month 24
Aim 1	Informed Consent	X						
	Updating of contact details and preferences	X	X	X	X	X	X	
	Demographic and disease data	X						
	Confirm ART regimen		X					
	Randomization to condition		X					
	Questionnaire		X			X		X
	Wisepill dispensing		X					
	Viral load (Study)		X				X	
	Viral load (SoC)			X		X		X
	IDI*		X			X		X
Aim 2	Questionnaire			X				X
	IDI**			X				X

* In-depth interviews (Aim 1): Include 60 participants (20 per site) at months 0, 12 and 24 (3 serial IDIs per person).
** In-depth interviews (Aim 2): include 30 people (10 per site) and up to 8 key staff per clinic at two time points during the study (2 total IDIs per person).

Visit windows

Screening and month 0 (enrolment) must take place within 6 weeks of the ART start. Study specific visits occur at months 4 (window open from months 2-6), 8 (window from months 6-9), 12 (window from months 9-15), 18 (window from months 15-21) and 24 (window from months 24-27); and will be synchronized wherever possible with routine clinic visits. Visit windows will be continuous, with each window extending to the midpoint between the last and current visit target date.

To achieve Aim 2, we will conduct an implementation science evaluation. While the effect of each combination of interventions on viral suppression and secondary outcomes in Aim 1 is critical, translation of potential benefit into real world impact requires understanding the implementation process. Among possible choices, we have chosen the Proctor evaluation framework[44] to guide this work as it enables measurement of implementation outcomes in relation to intervention outcomes, as well as impact on clients.

Per the Proctor framework, we will assess implementation, service, and client outcomes. Service outcomes will be generated from trial data and will not require additional data collection. Data collection for the implementation and client outcomes, as detailed in the Data collection section, will involve brief questionnaires for trial participants and clinic and study staff at two time points, as well as clinic record audits and clinic observations. We will also collect data on costs, and conduct IDIs with both participants and clinic staff, as detailed below under data collection.

In our final analyses (Aim 3), we will need to understand the utilities attached to individual implementation and client outcomes. We have added into Aim 2 activities a discussion with CoCT officials to collect their views on utilities. Two experienced members of our team will meet with CoCT officials and apply RAND/UCLA modified Delphi panel consensus methods, as used as used previously by Dr. Gifford in the LEAP study.[45-47]

Time required for trial participants

We estimate that the time required for study participation above and beyond completing questionnaires at the three time points described above will be minimal. The monitoring components of the trial (adherence and retention) each require very little if no time on the part of the participant other than accepting and engaging in outreach via text / WhatsApp / phone call if nonadherence is detected. If that happens, and the participant is identified as nonadherent to his/her ART medications by the assigned monitoring method/s, the patient will be asked to engage in the core Risk of Treatment Failure standard of care adherence support program, as well as one or both of the support components, depending on assignment to condition. This time will depend on the specific experimental condition assigned to the patient, but our rough estimate is that the weekly check-in texts (support component 1) may require 2-15 minutes per week over 16 weeks, depending on whether the participant asks for a follow-up call. The enhanced peer group counselling component (support component 2) is unlikely to require much more time beyond the time devoted to standard of care peer groups (these two are alternatives, so any participant would have one but not both). Both versions of peer group support involve a total of 4 sessions over a 4-6 week period, so any additional time due to the motivational interviewing methods used in the enhanced version of this support should be fairly minimal (10-20 minutes per session at most). Thus, none of the intervention components require a major additional time commitment by participants.

Aims 1 and 2: Delivery of components and fidelity assessment

Each clinic will provide intervention components. Clinic staff will deliver the SoC including the basic adherence counselling (**S2-B**) with retraining on these these activities provided during start-up, to ensure SoC is delivered. As noted above and in the attached "GRO COVID Plan" document, staff will have been trained in and will follow all locally-relevant and recommended protective activities.

Full-time on-site Community Research Workers (CRWs), as well as other study staff, will track delivery of adherence monitoring components (**M1, M2, M3**) and time spent beyond current practice using REDCap (extra time spent will be considered in Aim 2 analyses and final component selection). They will also deliver **S1** (through the Wisepill system) and **S2-E** using a detailed manual developed for this purpose.

Fidelity assessments will be conducted by the study coordinator using a two-pronged approach with regular reports to the investigators: a) monthly REDCap reports generated by the data manager will be reviewed to assess intervention delivery and b) quarterly random clinic observations will assess quality of delivery and participant engagement (10% of patients/site). Any errors will be corrected immediately and noted for analysis.

Aim 3

The goal of this aim is to utilize the data from Aims 1 and 2 to determine an optimal packaged intervention for PLWH at community clinics in Cape Town. Using effect sizes and cost data, we will

identify the most cost-effective combinations of intervention components. We will then incorporate key implementation and client outcomes to tailor the intervention selection to the priorities of the end users.

E2. Data collection

For trial participants, data collection will take place via the following activities:

1. Aim 1 Quantitative data collection via questionnaires at 3 time points: months 0, (enrolment), 12, and 24 (study completion). The questionnaire at baseline will also include basic background socio-demographic information (gender, age, marriage status, education, employment). These questionnaires will ask about a range of behaviors and aspects of life for patients that may affect ART retention and adherence including: stigma, depression, substance use, and gender inequity. We will also ask about topics that relate directly to the adapted self-determination theory that informs the study. These relate to autonomy support, social support, knowledge, as well as motivation and self-competency. We expect each questionnaire to require 45 minutes to 1 hour to complete.

2. Aim 2 Quantitative data collection via brief questionnaires: at two timepoints: 1) at month 12* (which we define as at month 12, or, if found to be nonadherent between month 0 – month 12, then at 12 weeks after nonadherence identification (+ or – 4 weeks); and 2) at month 24. (Please also see Table 2 for data collection for Aim 2 outcomes.) These will query selected questions related to implementation outcomes and client outcomes (e.g. acceptability, appropriateness, feasibility, satisfaction). We expect each questionnaire to require 45 minutes to 1 hour to complete.

3. Viral load tests above and beyond standard care for Aim 1: enrollment (month 0) and month 18. Per standard of care, viral load tests are performed at months 4, 12, and 24, so we will only add two additional tests for this study (participants will thus have five tests done rather than three over this 24-month period. All standard blood draw and testing procedures will be employed for each blood draw). All viral load tests will be performed according to nationwide approved procedures at the National Health Laboratory Systems (NHLS) in Cape Town. At each blood draw, 5 mL of blood will be drawn. We will use results per Standard of Care nationally using <50 copies/mL as the threshold for undetectable virus. A raised (detectable) viral load test result will generate a call / outreach in all conditions.

Aim 1 Qualitative data from a subset of trial participants: months 0, 12, and 24. A subset of 60 participants (20 per site) will be invited to participate in serial IDIs in order to collect open-ended data on potential mediators of key outcomes. The will include questions regarding stigma, depression, substance use, and gender inequity, and are designed to supplement the quantitative questions collected via annual questionnaires. We estimate that each interview will take 45 minutes to 1 hour to complete. Each will be audio recorded for later transcription, translation, and analysis. We will select a subset of the main cohort who have self-reported prior experience with substance use, depression, gender inequity, stigma, or transport/clinic issues in our baseline questionnaire. We will select purposively from this subset so as to collect qualitative data across gender and age ranges.

4. Aim 2 Qualitative data from a subset of trial participants: at two timepoints: at month 12* and again at month 24. An additional subset of 30 participants (a targeted selection of 10 participants from each clinic, none of whom will be among those participating in the Aim 1 serial IDIs, to keep the time burden to a minimum) will be invited to participate in an in-depth interview. The questions will focus on

subjects' experiences with the monitoring and support component of the study intervention, including the experience of being 'watched' by the EAM and/or the PRM. We will probe issues that relate directly to key features of implementation of the intervention, including the specific supports provided during the SoC adherence support (Risk of Treatment Failure) clinics. This will enrich and help validate the quantitative data we will collect on these topics and inform our understanding of how the different components impact on the experience of being a patient at a community clinic in Cape Town. We estimate that each interview will take 45 minutes to 1 hour to complete. Each will be audio recorded for later transcription, translation, and analysis.

5. Adherence data monitoring: Each EAM device used by a study participant will provide continuous data on openings (a proxy for adherence) with automatic reports for those in conditions that include **M3/EAM** (for others, EAM will be passive). Study participants need do nothing but store their ART tablets in the device and take one from it every time they take a tablet.

6. Retention data monitoring: PRM data will be produced for all participants by each clinic's pharmacy database (known locally as iDART). Reports will be generated for those in conditions that include **M2/PRM** (for others, PRM will be passive). For participants, this will involve no extra steps or interaction with study staff.

7. Time to nonadherence detection/link to support:. We will use data from the monitoring tool that first detects nonadherence (M1, M2, M3); 'link to support' will be noted in ROTF clinic records and used in analyses.

Data collection among staff (clinic staff and study staff) at the study clinics:

1. Quantitative data collection via questionnaires for Aim 2: at two time points (month 8-9 and again at month 32-33). These will query selected questions related to implementation outcomes and client outcomes (e.g. acceptability, appropriateness, feasibility, satisfaction). We expect each questionnaire to require 45 minutes to 1 hour to complete.

2. Qualitative data collection via IDIs for Aim 2: at two time months (same as quantitative data collection). We will invite 5-8 key clinic and study staff members from each clinic (15 total) to participate in IDIs at these two time points when we will conduct similar IDIs with study participants. As with the IDIs with trial participants, we will probe issues that bear on elements of intervention implementation to inform feasibility and acceptability of the specific intervention components. We estimate that each interview will take 45 minutes to 1 hour to complete. Each will be audio recorded for later transcription, translation, and analysis.

Additional data will be collected via clinic records and observations for Aim 2 (see Table 2).

Table 2: Aim 2 outcome measures and data sources

(excluding service outcomes, which will come from the trial)

Implementation outcomes	**Measure**	**Data source**
Acceptability	Acceptability of Intervention Measure (AIM) - 4 items with 5-point ordinal response	Participant and staff questionnaires, IDIs
Adoption	Intervention uptake by patients	Audit of clinic records
Appropriateness	Intervention Appropriateness Measure (IAM) - 4 items with 5-point ordinal response	Participant and staff questionnaires, IDIs
Costs	Microcosting, time and motion studies; unit costs will be extrapolated from Eaton et al.[49]	Clinic observation (once; in 2-week blocks at each clinic)
Feasiblity	Feasibility of Intervention Measure (FIM) - 4 items with 5-point ordinal response options[48]	Participant and staff questionnaires, IDIs
Fidelity	1. Of intervention implementation: adherence to protocol, exposure to appropriate intervention. 2. Of intervention content: intervention delivered correctly (e.g checklists, review of group support sessions; see Section 4 for examples)	1. All records; monitored monthly via RedCap; queries generated, deviations recorded and investigated. 2. Clinic observations (random 10% of patients per clinic, performed quarterly)
Penetration	Percent of participants receiving the intervention when indicated	Audit of clinic records
Sustainability	Change in all implementation outcomes for months 4 - 24	Audit of clinic records and participant and staff questionnaires
Client outcomes		
Satisfaction	Satisfaction survey[50,51] - 12 items with Likert ratings, validated in South Africa (e.g., respect, info provided, wait times)	Participant and staff questionnaires, IDIs
Function	Perceived reduction in effort to achieve viral suppression	Participant and staff IDIs

*Note: AIM, IAM, and FIM will be used for the monitoring and support strategies separately.

The questionnaires and IDIs were described above. The additional data collection for Aim 2 is summarized in Table 2 and described below.

1. Clinic record audits will take place monthly throughout the trial. These will generate data to address specific implementation outcomes:
   a. Adoption (participant uptake of interventions to which they are randomized);
   b. Fidelity (are procedures being following for delivery of each intervention? And are participants being exposed to the interventions to which they were randomized and not ones to which they were not randomized);
   c. Penetration (percent of eligible patients enrolled); and
   d. Sustainability (change in implementation outcomes between the two times of data collection (at M12* and month 24).

2. Clinic observations will take place as follows:
   a. For the cost outcomes, we will conduct one two-week time and motion study at each clinic once it is operating at a steady-state (between months 6 and 12) to determine the time needed for each intervention. Facility manager approval for these activities will be formally requested from the City of Cape Town at the time of application for this study. Multiple visits during this two-week period for each sequence of components will allow estimation of the average time for each step. Time for research purposes (e.g., data collection) will be noted separately from estimated time for implementation. Multiple staff (clinic and study)will be observed and interviewed briefly to capture the range of time and extent of effort required for each step.

   b. For the fidelity outcomes, we will supplement the clinic audits with random clinic observations of 10% of participants each quarter. These will aim to track what happens to participants as they participate in various interventions (that is: do they attend a given counseling session when they should attend it? Do they stay for the entire counseling session? Do any issues arise that suggest lack of fidelity to the intervention as designed?).

3. FGD with CoCT policy-makers:

In order to collect the utilities needed for final Aim 3 analyses, we will also conduct one FGD with officials at the COCT. The purpose of the FGD is to gain insight into the utilities with which key stakeholders view specific implementation-related outcomes, such as cost, sustainability, and acceptability. We have worked closely with these stakeholders and they are prepared to collaborate on this exercise.

The FGD will be held with 4-5 stakeholders at the COCT who represent different aspects of the health care system: clinic, district manangement and senior management (e.g. HAST committee). Basic demographic information will be collected (age, gender, education, position, length of time in position at COCT). We will then apply RAND/UCLA modified Delphi panel consensus methods as follows: we will ask participants to pre-rate utility outcomes by high vs. low importance, with scaleability in mind; discuss the relative value of outcomes in policy-making for HIV care; and hold a final discussion of ratings involving use of ordinal card-sorting for consensus in determining the utility levels for each outcome.

The FGD will be held at a location convenient to the officials. We will audio-record the FGD, and also take field notes to assist with any questions of interpretation and/or meaning. We anticipate that it last 60-90 minutes.

Two experienced members of our team (Dr. Gifford and Dr. Haberer) will conduct the FGD.
There will be no follow-up data collection associated with this study.

<u>Data collection staff and training for Aims 1 and 2</u>

Data will be collected by DTHF study staff with previous experience conducting similar research. Prior to beginning data collection, a 3-5 day training workshop for study staff will be led by Dr. Orrell/Jennings, with likely assistance from members of the Boston-based team (depending on SARS-COV-2 travel restrictions). The workshop will include detailed discussions of study participant recruitment, the informed consent process, and other ethical issues, including confidentiality and privacy matters. The training will reinforce all ethical issues regarding research involving human subjects and ensure that

study staff understand and will be in a position to follow appropriate enrollment and data collection procedures for this study. For this purpose, we may make use of PowerPoint slides on the protection of human subjects that we will adapt for this study (see attached PPT slides). Study staff will practice procedures such as obtaining informed consent until we are confident that procedures will be conducted appropriately. A log will be kept onsite with the names of research staff who have been trained and the date on which they were trained. This log will be updated continuously and will be available for review at any time. During this process, quantitative questionnaires and IDI guides may be modified, if considered appropriate, by the research team. We will seek approval from BUMC and University of Cape Town IRBs for any changes made to these guides before the local study team uses the instruments for data collection purposes.

Aim 3 data collection

There will be no additional data collection for Aim 3. It involves analysis of data collected for Aim 1 and Aim 2.

PART F: Sample Size/Data Analysis

F1. Sample size

Trial participants

The study is powered to detect clinically meaningful individual main effects of intervention components on HIV viral suppression. As shown in Table 3, the estimates of observable difference (with a two-sided alpha of 0.05 and 80% power, and prior to any clustering effect) that we expect to find with a sample size of n=382 range from 11% to 15%, depending on viral suppression in participants receiving/not receiving a specific intervention component. Recent work at Cape Town clinics indicates suppression rates of 51-79% at month 12 post-initiation of ART.[4] Conservatively, if viral suppression is 60% at 24 months in participants not receiving or receiving the lesser intensity of a component, we will be able to observe a difference of 14 percentage points with n=382, a difference with clear clinical significance. To take clustering into account, we do not know the intraclass coefficient component (ICC) for each clinic, but will conservatively assume they are 0.15, leading to an increase in sample size of 20% (or n=458). To account for lost to follow-up of up to 10% (based on recent study site experience), we will recruit a total of n=512 participants to ensure complete data for n=458 participants. For secondary outcomes, this sample size will allow us to detect differences in ≥90% adherence and in retention of 11%-15%, a meaningful range that is reasonable given other studies.[42,52]

Table 2. Detectable difference in HIV suppression and ART adherence (alpha = 5% and 80% power).

Analysis/ Outcome	Condition without component	Condition with component	Percentage point difference
% HIV suppression at month 24	40%	55%	15
	51%*	66%	15
	60%**	74%	14
	70%	83%	13
	79%***	90%	11
% ≥90% Adherence at month 24	20%	34%	14
	35%	50%	15
	50%	65%	15
	60%	74%	14
	70%	83%	13

* % HIV suppression at Mo 12 in pregnant women, META[3]
** % HIV suppression at postpartum month 3, WiseMama[131]
*** % HIV suppression at Mo 12 in late ART starters, META[3]

The total sample size of patient participants is thus 512. Among that total, two subsets of 30 will be selected for participation in IDIs at various timepoints.

Sample sizes of clinic staff

The total sample size of clinic and study staff is 24 (maximum) (brief questionnaires and IDIs at two time points). Among them, we will select 5 clinic and study staff per clinic (based on those most involved in the interventions) to participate in IDIs.

The sample sizes for the IDIs were chosen based on feasibility and timeline. Based on our experience in prior qualitative studies, we will be able to generate themes to add rich and meaningful detail and personal experience to the quantitative data collected for the study.

Sample size for FGD with COCT officials

We will enroll up to 5 COCT officials for the FGD.

Thus, our total sample size is 541 (512 patients, 24 clinic and study staff, and 5 COCT officials).

F2. Access to this population

Dr. Orrell and her team have been working in the clinics selected for this study for many years, and have encountered few problems. These clinics were selected on that basis, to ensure smooth implementation of the study by an experienced local team. Prior to submitting our project proposal, we discussed the study with the clinic supervisors and they are comfortable collaborating on this study. BUSPH researchers will collaborate as much as possible and help problem solve, but the local team led by Dr. Orrell will be responsible for interaction with both clinic staff and patients for this study. Each of the three study clinics has large numbers of new HIV-positive patients every year (450-600+ in recent years). A high proportion will meet our eligibility criteria. We need to recruit 170 patients from each clinic over 18 months (<30% of those eligible); which is feasible and supported by the numbers.

F3. Outcomes

Our outcome measures are summarized below by Aim:

Aim 1: Primary outcome

Viral suppression at 24 months. % plasma VL <50 copies/mL (dichotomous).

Aim 1: Secondary outcomes

a. Viral suppression at 12 months: % plasma VL <50 copies/mL (dichotomous).

b. Change in Viral Load: Mean change in HIV plasma, month 0 to month 12 and month 0 to month 24.

c. Days of unsuppressed virus: # days between months 0–24 (for those suppressed at M4); same at each month 4, month12, month 18, and month 24 timepoint; # of days between any two consecutive dates of unsuppressed virus.

d. Adherence: % ≥ 90% and ≥ 80% adherence in month 12, and month 24; mean adherence in month 1-12 and in month 1-24.

e. Time to nonadherence detection with link to support: # of days from month 0 to day detected as nonadherent; #of days from month 0 to linkage to support (at ROTF clinic).

f. Retention: % attending all refill visits (within 7 days) in month 1-12 & month 1-24; % attending ≥ 75% refill visits (within 7 days) in month 1-12 & month 1-24; % lost to care, defined as no clinic contact identified for ≥ 90 consecutive days at month 24.

g. Additional constructs and variables (from Self-determination Theory and moderating variables) for use as covariates.

h. Additional data on potential moderating and mediating variables: Using surveys and IDIs at enrollment and months 12 and 24.

Aim 2: Implementation outcome measures

(top tertile of each scale will be considered "successful"): a) acceptability, b) adoption, c) appropriateness, d) costs, e) feasibility, f) fidelity, g) penetration, and h) sustainability. Specific outcome measures are contained in Table 2.

Aim 2: Client outcomes measures

(top tertile of each scale will be considered "successful"): a) satisfaction, and b) function. Specific outcome measures are contained in Table 2.

Aim 2: Utilities for final cost-effectiveness analyses

Each implementation outcome will be given a 1/0 value, based on the utility policy-makers determine in the FGD.

Aim 3: Cost effective package

We will not have a specific outcome measure, but we use the utility-related information we gain in the FGD with COCT officials to inform a final decision on recommendation of the most cost-effective and scalable intervention package.

F4. Data Analysis

Dataset preparation, basic approach, and missing data

Data captured in REDCap will be exported to SAS for all quantitative analyses. Overall, we will adopt an intention to treat (ITT) analytic approach for data analysis, similar to other studies of this type.[3,53] We will first calculate descriptive statistics of all study variables (means, ranges, standard deviations for continuous variables; percent data missing, frequencies and percentages for categorical variables). Missing baseline data on socio-demographics will be imputed using a single, or multiple imputation technique if the proportion missing is <10%, or ≥10%, respectively. In cases of missing VL data, we will treat the result as detectable, in accordance with our primary ITT analytic approach, similar to other studies. In cases of missing adherence data, the most recent month's adherence will be used to estimate single-month adherence; for cumulative calculations, available data over the period will be used.

Primary analysis for Aim 1

The primary outcome is viral suppression at 24 months, measured as a binary variable, to allow us to assess a sustained 6-8 months post-intervention effect.[54] We will use logistic regression to estimate main and interaction effects on the odds of viral suppression. We will use an exchangeable correlation matrix, accounting for clustering by health facility for all analyses. Intervention components will be effect-coded. To estimate the main effect of an intervention component, we will multiply the coefficient term by two and exponentiate it. We will use the same approach to estimate interaction effects between components.

Secondary analyses for Aim 1:

Estimating effects on viral load suppression

We will use logistic regression to estimate effects of components on secondary outcomes measured as a binary outcome (VL at month 12; adherence; retention). We will use ordinary least squares or poisson regression to estimate effects of components on outcomes measured as a continuous variable (e.g., mean change in VL from month 0-12 and month 0-24) or count variable (e.g., days of unsuppressed virus), respectively. We will compare dropout rates and characteristics of participants who drop out or are lost to follow-up with those retained to assess potential for bias. We will also assess evidence of contamination by examining data from our detailed REDCap records and texting logs, using any such evidence when interpreting data on outcomes. Moderating effects will be explored through regression modeling following Hayes;[55] mediators will be assessed using the approach by Valeri and VanderWeele, which allows for logistic modeling, and sensitivity analyses will be conducted on key assumptions per Imai.[56,57]

Aim 1 qualitative data analysis

All IDIs will be recorded at the time of data collection, transcribed, and then translated into English. The resulting transcripts will be transferred to the Boston-based team for analysis via a secure system such as DataMotion, which we have used many times successfully in the past.

The serial IDI data (Aim 1) will be analyzed to examine potential mediating and moderating influences over time (e.g., reductions in substance use and stigma) using content analysis, involving iterative transcript review, label development, creation of operational definitions, and codebook development. We will doubly code ~20% of interviews and discuss discrepancies to achieve consensus between analysts. After codebook completion, transcripts will be coded in a qualitative data software (such as NVivo or Dedoose). We will identify direct statements to illustrate findings.

Aim 2 analyses

All quantitative implementation and client outcome data will be summarized using descriptive statistics (means, ranges, standard deviations for continuous variables; percent data missing, frequencies and percentages for categorical variables). We will examine the distributions for each outcome, and create tertiles for variables that use a scale (acceptability, appropriateness, feasibility, fidelity, satisfaction), variables expressed as proportion uptake (adoption, penetration), and retention (sustainability). Success for each outcome will be defined as the top tertile of the distribution.

For the cost outcome, we will first track costs associated with developing procedures (e.g., EAM acquisition, data management). We will then use the time and motion study data from clinic observations to estimate the time needed to implement each intervention. Next, we will assign costs to each utilized procedure and associated staff in a micro-costing exercise. Costing data will come from clinic account and publicly available sources, per Eaton et al. Analysis will follow the Clinton Health Access Initiative guidelines for costing HIV interventions, reflecting the health system perspective. We will use data from time and motion studies and micro-costing exercise to complete intervention cost worksheets. Costs will be categorized as fixed or variable for each intervention. We will also estimate the costs of combinations of interventions, where we observe time or other savings from performing activities in tandem.

Qualitative data from the IDIs with both participants and clinic and study staff will be analyzed for acceptability, appropriateness, feasibility, satisfaction, and function using a content analysis approach. We will apply the same detailed analysis methods described above for Aim 1.

Aim 3 analyses

We will identify the intervention components shown to be efficacious, taking main effect sizes and interactions into account. Estimates on durability of effect will be conservative for the main analyses (e.g., we will assume the same effect over 24 months as observed in the study). Using cost data from Aim 2, we will apply simulation modeling methods to identify intervention packages that improve health outcomes (e.g., HIV viral suppression) at the lowest cost over a 24-month time span (e.g., on the efficiency frontier of the cost-effectiveness plane). We will incorporate estimated downstream and current costs, following guidelines by the Panel on Cost-Effectiveness in Health and Medicine.

The main analyses will assume a payer perspective and a 3% discount rate. Sensitivity analyses will explore the impact of uncertainty on key variables, varying the probability distributions of each factor as well as the time horizon. We will consider 5-year and 10-year time horizons, as well as different perspectives (payer and societal), and examine the effect of different discount rates (0%, 5%) as recommended by Gold et al.

The cost-effectiveness (CE) analyses will be guided by the Proctor framework. Thus, we will determine an "adjusted CE outcome" (AdCE) for each intervention condition as a function of CE plus implementation and client outcomes defined in Aim 2. We will apply utility levels obtained from key stakeholders, incorporating the value they attach to each implementation outcome, and calculate AdCEs using the following equation:

$$AdCE = CE / (IO_1U_1 + \ldots + IO_8U_8)$$

where CE = cost-effectiveness, IO is the success score of specific outcomes, and U is the utility of each outcome. Utilities will be expressed dichotomously (high value = 1; low value = 0) for simplicity and clarity. Thus, a given CE outcome may be more (or less) valued in the context of higher (or lower) implementation outcomes (e.g., acceptability and adoption), all other factors being similar.

After the modeling exercises, members of the core team will identify the options that best combine a positive effect, low cost, and implementation priorities, including staff time required, eliminating poorly performing and costly elements. The resulting options will be discussed with key stakeholders in Cape

Town using a discrete choice approach to determine the final, optimized intervention (likely with 2-4 components).

PART G: Potential Risks / Minimizing risks

G1. Potential Risks

Aim 1:

The patients who participate in SUSTAIN will all be individuals with HIV infection, and as such constitute members of a vulnerable population at special risk. The explicit goal of the study is to assess the usefulness of various combinations of the five adherence monitoring and support components in achieving viral suppression and maintaining retention in care. The study does not involve any experimental medication beyond what is the current standard of care for patients in South Africa, and only two additional blood draws for viral load at enrolment and month 18 (above standard of care as explained above). The volume of blood provided will be 5-10ml, similar to that currently drawn for viral load monitoring. However, participation in the study may involve several possible risks and/or inconveniences. Below we detail these potential risks and explain our procedures to minimize each one.

A first possible risk is that the HIV status of a patient will be inadvertently disclosed to someone beyond the ART clinic or study team. Although such disclosure of HIV infection can lead to a stronger support network for a patient, it is important to recognize that such disclosure may result in undesirable effects such as social stigma. This is a major concern given that people living with HIV, including the adolescents who participate, may be in situations (work, school, youth activity, etc.) where the repercussions of inadvertent disclosure could be quite negative. This will be minimized through the use of unique patient identifiers for all data and case report forms, as well as on study laboratory forms. All study staff are aware and trained in the management of confidentiality.

A second possible risk of participation relates to use of the EAM. This device poses no physical risk because it performs no direct therapeutic function, does not enter a patient's body, and is not a drug. However, it is possible that some subjects may find it strange or uncomfortable to use a box that monitors their pill-taking behavior, or that knowledge of the EAM by others may increase social stigma or result in inadvertent disclosure of HIV status.

A third possible risk is associated with the blood draws that will be done in order to conduct the viral load testing. As with any blood draw, this involves a small needle stick, and there is the minimal risk of bruising or bleeding at the site, and the risk of infection. These risks are present with every blood draw, and as per standard of care, the usual clean practices for phlebotomy will be employed to minimize risk of infection and bleeding. We are asking subjects to engage in two additional blood draws, but these will be drawn by the CoCT nurses using the same processes as for standard of care.

Fourth, risks of study intervention components. Participants in all 16 conditions will be called on their phone (or contacted via other methods that they indicate are acceptable such as texts, WhatsApp) should they meet the criteria set out for finding nonadherence. This is not standard of care clinic practice and will be clearly explained during the informed consent / assent process. Study staff are trained in managing study procedures with confidentiality and will not reveal the identity of any participant or the reason for the outreach should the participant not be the one responding to outreach. The enhanced peer support

group component will be delivered by trained CoCT staff in the clinic (instead of the basic standard of care peer support) so should not increase risk in itself. The weekly check-in text messages, for those assigned to receive them, will contain impersonal messages that will not mention disease or anything related to HIV.

Fifth, there is also a risk of inconvenience related to the time required to provide information in the questionnaires at enrollment and months 12 and 24 and via the IDIs at the same time points for a selected subset of participants (n=30). We are mindful of this inconvenience and will do our best to keep this time to a minimum.

Sixth, there is the possibility of emotional upset while completing a questionnaire or IDI. Discussing some aspects of their lives, experiences with the study, or other facet of being HIV positive may well cause anxiety for the patient participants. We will do our utmost to be sensitive to this possibility and to offer any subject who becomes upset a chance to pause, not answer, or even withdraw from the study if the subject so desires.

Seventh, there may be some additional risk of SARS-COV-2 infection, depending on the vaccination situation in Cape Town at the time of study implementation. While it is our hope that vaccination rates will be high for the local population when we start enrolment in early 2022, we are prepared for a less-positive situation. Thus, participants who are identified as nonadherent and referred for support activities may need to travel more often than otherwise, and come into close contact with more individuals than otherwise (for instance, during peer support group meetings), thereby putting themselves at higher risk of infection if they are not vaccinated. Similarly, participants selected for additional serial IDIs will have additional close contact with study staff. All appropriate protective measures will be in place (see below), but participation does represent additional risk.

Aim 2:

Risks five, six, and seven above would also relate to the questionnaires and IDIs at various times (for both patient participants and for clinic and study staff). There is the possibility of emotional upset while discussing interventions to support ART. Discussing challenging situations they face while providing HIV care and treatment may be upsetting for those clinic staff who participate in an IDI. We will do our utmost to be sensitive to this possibility and to offer any subject who becomes upset a chance to pause, not answer, or even withdraw from the study if the subject so desires. There is also some additional risk of SARS-COV-2 infection from close contact with study staff. Appropriate protective measures will be followed, as explained below.

For study staff who participate, there is also a risk of potential coercion to participate and some risk that what they say about study implementation will be overheard or learned about by others. We will reduce this risk as much as possible by adopting special procedures for data collection with study staff (see below).

Risk five above, inconvenience, is the main risk for the COCT officials who participate in a FGD. We recognize that, for busy officials, it may be a burden to join in this exercise. As with all data collection activities, we are mindful of such inconvenience and will keep the time required for participation to a minimum. Additionally, there may be additional risk of SARS-COV-2 infection due to close contact with study staff. We expect that all participants will have been vaccinated, but there may still be some small

additional risk of infection. Appropriate and comprehensive protective measures will be followed, as explained below.

G2. Minimizing risks

We will minimize all risks associated with study participation to the greatest extent possible. Before any recruitment for the study occurs, the study materials (including protocol, data collection instruments, informed consent, and assent forms) will be approved by: (1) the University of Cape Town Research Ethics Committee; (2) the City of Cape Town Research Committee; and (3) the Boston University Medical Center Institutional Review Board (IRB).

All potential participants in the trial will undergo informed consent procedures, including emphasis that participation is voluntary and that refusal will have no negative impacts on the ART service they receive at their clinic. Adult eligible participants aged 18 years and over who agree to enroll in the study will provide full written informed consent. Eligible adolescents of ages 16 and 17 years will not be able to enroll unless they are willing to complete an assent form and are able to bring a parent or guardian with them to complete a parental full informed consent document. All informed consent and assent processes will be conducted in the language of the participants choice (usually English or Xhosa); and the forms will be available in these languages as well. The informed consent and assent document will contain contact details for study staff who are available to answer questions about the study.

Once enrolled, each trial participant will provide contact / locator information which will be updated at every study visit so that he/she can be contacted by phone as per their assigned component. Each will receive a unique identification number to link to study data generated for him/her. Only the study staff will be able to link the patient with the study number. No patient identifiers (name, address, contact details) will leave the study site.

Here we provide a description of our efforts to minimize all risks. First, during the consent process for each set of activities, we will do our utmost to ensure that all potential participants as well as their guardians (for adolescents) understand the truly voluntary nature of their participation, and that they are able to withdraw at any time, for any reason, without fear of any change in their relationships with or care from the providers at the study clinics.

Second, we will attempt to minimize specific risks in the following ways.

<u>a. Patient confidentiality (Aims 1 and 2).</u>
We will ensure the confidentiality of all subjects to the greatest degree possible throughout the study. All collected data, including written documents and audio recordings (IDIs only), will be kept strictly confidential. Data files, audio files, transcripts, questionnaires, and forms will all be kept locked at all times when they are not in use by study personnel. Subjects will each be assigned and identified only by a unique ID number, as will the parent/guardian in the case of minors, whose ID number will be associated with the adolescent for whom they provide care. Subject names will not be entered into analytic databases. A single master log sheet linking patient names to unique numbers, and the locator files that the study will maintain to be able to contact participants, will be kept under strict lock and key at each study site. These will be destroyed after the subject completes the study or a final disposition is known (died, withdrew, lost to follow up). The study number alone will identify all forms containing the results of adherence monitoring, clinical examinations, laboratory tests, and questionnaires.

All paper questionnaires, EAM devices, other computer-based data files, and audio recordings will be accessible to named study personnel only, and only in forms without identifying personal identification of any kind other than the unique study ID number.

A dedicated transcriptionist trained in research ethics will translate and transcribe (verbatim) data collected on digital audio recordings from the IDIs. All IDI recordings will be stored on a password protected and encrypted hard drive, and destroyed after the patient completes the study or a final disposition is known about the patient.

Study data from the clinic site will be entered and maintained on a secure, online, and password-protected database on a REDCap platform, linked to a secure web-based platform, from which data can be downloaded to a secure database at BU for analyses. Regardless of language, there will be no personal identifiers on any of the data sets. Computer-based data will all be maintained in password-protected files in encrypted folders, and the document that links names and study numbers will be stored in a locked office, with access limited to key study personnel. All computers with study data will be kept password protected.

Study results and analyses presented in technical reports, manuscripts, and articles, including qualitative data, will either be presented in aggregate form, or with details removed to prevent identification of individuals.

Throughout the study, MPI Dr. Orrell (or Dr. Jennings, the site investigator) and counsellors will be available for counselling regarding potential or actual disclosure of HIV status. If any subject should fear or suffer from stigma and/or violence related to disclosure of their HIV status, study team members will intervene to provide support, including arranging for hospitalization and treatment and contacting other health officials and local public health or police authorities, if appropriate.

Given our previous experience in South Africa, we expect that these strategies will be effective in protecting against and minimizing potential confidentiality risks. Our MPI Dr. Orrell has conducted this type of research for nearly 20 years in Cape Town and thus has extensive experience working with HIV-positive patients and maintaining their confidential information, and has an excellent record for following these procedures.

<u>b. Minimizing risks related to use of EAM Devices (Aim 1)</u>
To reduce the risk that discomfort with these devices might negatively affect adherence among the patients, the nature and purpose of the devices will be clearly explained during the informed consent process so that any patient who is uncomfortable with the idea of using one will be able to decline participation in the study. If a study team member suspects that the device is causing a patient serious discomfort or worsened adherence, a team member will arrange to discuss this with the subject. Dr Orrell and her team have extensive experience with the use of these devices at site (in over 1600 participants since 2012), and to date the devices have been acceptable, and the risks have been few.

<u>c. Minimizing risks during blood draws (Aim 1)</u>
To minimize the risk of bruising and infection at the site of the needle stick, standard clean procedures for keeping adverse reactions to a minimum will be used in all three study clinics. Bloods will be drawn by staff trained in phlebotomy.

d. Minimizing risks related to adherence intervention (Aim 1)

To reduce the risk of disclosure or other risk or inconvenience during the intervention monitoring or support components, the details of what the support entails will be carefully discussed with the subject in advance, with careful attention to ensuring that the patient understands all the elements of their assigned condition (a combination of up to five components). Later, if any study team member believes that a patient is being negatively affected by their condition, or if a patient complains of anything, our local MPI Dr. Orrell, or site investigator Dr. Jennings, will be contacted, and the matter will be discussed with fellow MPI Dr. Sabin.

e. Minimizing inconvenience related to the study (Aims 1 and 2)

All possible efforts will be made to keep the time required for completing the required study questionnaires and IDIs as short as possible. As few procedures in addition to standard of care have been added as possible.

f. Minimizing the risk of emotional upset during data collection (Aims 1 and 2)

We will do our best to be sensitive to the mood of subjects during data collection. If a subject becomes upset during a survey or interview, he/she will be given a chance to wait until he/she is ready to continue. Study staff will have been trained in data collection techniques and this will include being attuned to these situations and being comfortable asking if the subject would like to wait, not answer, or even come back at another time. In extreme situations, the subject will be asked if withdrawal from the study would be what the subject would prefer. At all times, participation is voluntary, and this basic principle will be upheld throughout the study.

In addition, we note that, based on our team's experience working in this local environment, we believe the risk of suicidal ideation or self-harm or harm to others is very low, and most likely unrelated to the study, which is designed to provide support to struggling HIV patients. While these CoCT clinics do not have dedicated mental health staff on site every day, participants with suicidal ideation or risk of self-harm can be referred into the mental health system through the larger Provincial Department of Health Community Health Centers, which accept psychiatric admissions at their 24-hour casualty unit, as well as by referral to the Mental Health nursing sister. Should the participant require admission after assessment, he/she would be referred to a tertiary hospital, Tygerberg or Groote Schuur. These procedures are aligned with standard research practice in Cape Town.

g. Minimizing the risk of SARS-COV-2 infection (Aims 1 and 2)

We are mindful of the very real dangers posed by SARS-COV-2 to all individuals. Recognizing the risk of infection to patients, medical providers, and others involved in research, there are protective measures now in place at all locations where the study will take place in Cape Town. They include: offer of vaccination for all clinic staff and all patients meeting eligibility criteria for the national vaccination program, adequate PPE (personal protective equipment) for all staff, conveniently-located hand sanitizer and soap in buildings, cleaning of surfaces before and after work activities in buildings, physical distancing inside buildings, and mask-wearing and COVID 19 screening prior to entering buildings for patients (please also see attached GRO COVID Plan). For our study, to keep infection risk at a minimum, we will ensure that all these measures are in place and are practiced by our study staff and by participants in the study when at study clinics.

h. Minimizing risks for study staff (Aim 2 quantitative and qualitative data collection)

To minimize potential coercion to participate and loss of confidentiality, we will ask another researcher outside our study team to recruit, obtain consent, and collect data from study staff for Aim 2 activities.

The researcher may play a minimal role in the project in terms of ensuring fidelity of study processes, but will not report to the PI. This researcher will approach and recruit the study staff, stressing that participation is voluntary to minimize the risk of coercion.

Study staff who participate will be given a unique ID #. The study team (PI and her team) will not know who agrees/refuses to participate. Subsequently, RAs and other study team members aside from the PI and the study coordinator will not have access to the secure hard drive where all IDI recordings and transcripts (for Aim 1 and Aim 2) will be kept. The transcription and translation of the study staff IDIs will also be done by an external group. For the short survey data, these data will be collected on hard copy (not via REDCap) and data clerks at the DTHF will input data from the hard copy CRFs into Excel (with only an ID#, and no identifying information). The Excel file will be kept on the same secure hard drive as the qualitative recordings and translated documents, to which the RAs will not have access.

Vulnerable Subjects (Aims 1 and 2)

Pregnant women will be included in this study, as they are a group at increased risk, across sub-Saharan Africa, of poor ART outcomes, usually due to poor adherence during pregnancy and poor maintenance of therapy in the early months after delivery. It is essential that adherence in this group is improved, in order to protect their own life as well as the lives of their current and future babies. Including these women is scientifically appropriate.

The pregnant women and their unborn babies will be at no increased risk through study participation. The study will not impact on the choice of ART made for the pregnant women. Through potentially improving adherence to ART, this research holds the prospect of direct benefit to both the mother and her unborn baby.

Similarly, we are including older adolescents aged 16 and above. These individuals are also at increased risk of poor ART retention and adherence and thus are being included purposefully. During the informed consent and assent process (both Aims 1 and 2), we will endeavour to be very clear what study participation entails so that these adolescents make an informed decision understanding the risks involved—and with their guardians - make the best choice for themselves.

PART H: Potential Benefits and Risk to Benefit Ratio

Potential Benefits

For all participants enrolled in the trial, there is the potential for improved adherence to their antiretrovirals as a result of the intervention/s. This improved adherence may lead to an increased proportion of individuals achieving viral suppression, with associated individual and public health consequences. In addition, this study is designed to generate generalizeable knowledge regarding the effects and cost-effectiveness of a package of practical interventions to improve rapid detection of poor adherence to HIV treatment and support for struggling patients. The findings may thus lead to improvements in HIV treatment policies and guidelines for delivery of HIV treatment that may affect large numbers of patients.

Risk to Benefit Ratio

There are a number of risks to subjects from participation. However, they are far outweighed by the benefit of better understanding of the effects and cost-effectiveness of a package of practical interventions to improve rapid detection of poor adherence to HIV treatment and support for struggling patients.

PART I. Data and Safety Monitoring

I1. Monitoring research safety of participants

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) – see defintion in section I2 - will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

I2. Data Safety Monitoring Plan (DSMP)

Overview of the DSMP

The US and South African MPIs together with the site investigator / medical officer (MO, Dr. Jennings) and the study coordinator (SCO), will monitor all aspects of data safety. Because this is a behavioral study that does not involve any testing of medications, or any type of procedure that is outside the usual care provided to HIV-positive individuals in South Africa, the study team's role in monitoring patient safety will be limited to mandated adverse event/serious adverse event/unanticipated problems reporting (detailed below) and alerting the clinics to unexpected test findings or conditions identified during subject participation.

To ensure the integrity of data collection and storage in South Africa, all study forms (paper or electronic) will undergo internal quality control e.g. through checking for completeness by the study coordinators, to ensure that missing or illogical data are corrected. Weekly updates on enrollment numbers, randomization allocation, and data collection will be sent to both MPIs for monitoring progress. Data completeness and quality will also be reviewed at least on a monthly basis by both Ms. Cogill, the South African site data manager, as well as by Dr. Halim, our chief analyst. The local team will

generate a quarterly data quality report describing the completeness of all data collection. Quality assurance practices will be completed by the MPIs, MO or designee (e.g. internal monitor) through a review of a 5% sample of all data newly collected every six months.

Reporting of adverse events and unanticipated problems

Our DSMP includes procedures for adverse events and unanticipated problems to be documented appropriately by the community research workers or on-site SCO and reported to the co-PIs in a timely manner.

Adverse events will include reported stigma or physical and/or mental harm as a result of participation in the study, including disclosure of HIV status. We will also record any clinical adverse event leading to a change in antiretroviral therapy. All adverse events will be recorded on designated forms and rated for both severity and seriousness.

Any serious adverse or unanticipated event that occurs during the course of the study which might be related to study participation will be reported immediately to one of the PIs. If the SAE is directly related to study participation these events will be reported to the IRB within two weeks of their occurrence; otherwise they will be reported on a 6-monthly line listing. The two-week period is necessary to allow the investigators to examine and clarify the full circumstances surrounding serious adverse events or unanticipated events. In collaboration with the local and US study teams, the MPIs will make a determination as to whether these events are probably, possibly, or unlikely to be related to study procedures. While all these events will be reported, they will need to be managed locally. When necessary, the study team can arrange for hospitalization and treatment at the nearest district hospital, though this is likely to be managed by the patient's own local clinic team.

All mild to moderate adverse events will be reported during the annual renewal of the protocol. Any events deemed by the BU team to be possibly related to the study will be carefully reviewed and, if necessary, modifications to the protocol or informed consent will be made in order to protect the safety of study subjects.

I3. Data Safety Monitoring Board (DSMB)

We will convene a DSMB for this study. The DSMB will be convened to assess the progress of the SUSTAIN study, the safety data and critical endpoints, and to provide recommendations to the MPIs. The DSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and data integrity of the study. Although the intervention is behavioral, the study will randomize 512 people to one of 16 experimental conditions, involving 5 intervention components, over a duration of 24 months and there is a potential that clinical outcomes in one of the conditions may be significantly better/worse than in the other conditions over that time. These outcomes might require independent ethical review.

In our experience conducting similar ART adherence trials in South Africa, Uganda, China, and Vietnam, we have experienced few study-related adverse events; and believe that the potential for study-related adverse or serious adverse events in this study remains extremely small so safety is unlikely to be the main focus of the DSMB.

We will convene a DSMB consisting of five members. The members would include individuals with experience in epidemiology, HIV and AIDS, clinical trials, and behavior change. The members of the DSMB will serve in an individual capacity and provide their expertise and recommendations. We will plan for a mid-point evaluation governed by the O'Brien Fleming Stopping Rules. If the DSMB's review of the mid-point review were to raise any concerns, we will immediately contact the City of Cape Town Health Management Team (HMT) In South Africa and work with them to develop a locally feasible and appropriate plan. The DSMB would also be provided summaries of all serious adverse events and unanticipated events related to the study every 6 months during the intervention period of the study.

PART J. Recruitment/Consent Procedures

J1. Recruitment

Aim 1 (randomized trial)

Participants in the trial (Aim 1) will all be HIV-positive patients, recruited from three City of Cape Town Primary Health Care Clinics. These clinics do not offer full curative adult care, but treat patients in disease programs: HIV care, including antiretroviral therapy, tuberculosis, contraception ("family planning"), and sexually transmitted diseases. They all have large numbers of new HIV-positive patients every year (450-600+ in recent years). A high proportion will meet our eligibility criteria. We need to recruit 170 patients from each clinic over 18 months (<30% of those eligible); which is feasible and supported by the numbers.

Potential participants will be first approached either at the point of HIV diagnosis, in the HIV Counselling and Testing (HCT) room, or when presenting for the first time to the ART clinic, and thus opening a folder. A study-employed community research worker (CRW), based in each of the clinics, will approach the potential participant briefly, and conduct a simple verbal prescreen describing the study, and inquire whether the individual is interested in hearing more. If the answer is yes, the individual will be invited to a private office space either on-site or in the Desmond Tutu Health Foundation (DTHF) Gugulethu Research Offices (situated within a few kilometres of all the recruiting clinics). At that point, screening will be done to ascertain eligibility and an offer of study enrolment will be made if the person is eligible. If the person still agrees, detailed informed written consent will be obtained. For adolescents, this same process will take place with the approval and agreement of both the adolescent and an adult guardian. The former will provide informed written assent, and the guardian will provide full informed written consent.

Aim 2 (participants in the trial, clinic and study staff, and policy-makers)

All patient participants in the trial will be asked to complete the short questionnaires for Aim 2 as part of trial participation; and all will be canvassed as to whether they might be interested in participating in an IDI during the initial informed consent process. A subset of patients who initially agreed to participate in the IDIs will be approached and again asked if they would be willing to participate. They will participate voluntarily and will complete a separate informed consent if they are willing to participate.

All clinic staff will be invited to participate in the Month 4 and 24 surveys. A subset will be selected for participation in an IDI. We will identify staff based on our goal of collecting data from a range of staff

who may have different perspectives and experiences, taking into account engagement with the interventions for the study. Our aim will be to have a diversified group of participants (by gender and age). These clinic staff will be approached by our study staff and asked about participation in the IDIs. These willing to participate will be enrolled in this component of the study.

For recruitment of study staff: recruitment: A socio-behavioral employee at DTHF, someone in a different group than our team at the DTHF, will recruit study staff. This person will not report to our study PI, but may have a minor role ensuring fidelity of study processes. The person will be relatively independent and thus capable of helping with this aspect of the study. He/she will approach and discuss possible participation in the study. He/she will be very clear when obtaining consent that participation is voluntary to minimize the risk of coercion. Participants will be given a unique ID #. The study team (PI and her team) will not know who agrees/refuses.

For the FGD with policy-makers, we will consult with our main contacts at the COCT on who would be best to include in this activity, in terms of ensuring a range of different perspectives. The goal is to include those officials who have the most authority in decision-making related to HIV treatment policy. Those we identify as most appropriate for this purpose will be approached by Dr. Orrell or by another study staff member in Cape Town by phone or in person, and asked about interest in participating. Participation will be voluntary and informed consent from each official will be obtained before the FGD begins.

J2. Recruitment

The PI confirms the following:

1. No direct or indirect remuneration that constitutes an inducement for recruiting or enrolling subjects will be accepted by any member of the research team; and
2. No bonus payments based on the rate or timing of subject recruitment or enrollment will be accepted by any member of the research team; and
3. Research involving medical services will comply with US federal and state anti-kickback laws and applicable anti-kickback policies of Boston Medical Center and BU; and
4. No payment or financial incentives (finder's fees) will be offered to any healthcare providers for referring patients to research studies.

J3. Consent Procedures

As described above, those potential participants who express interest in participating in the study will meet with a member of the data collection team to discuss the study, what participation will entail, and provide consent. Potential patient participants in the trial will have up to 6 weeks to decide whether or not to participate, depending on when they are approached (they must be enrolled not later than 6 weeks post ART-initiation). The voluntary nature of participation will be emphasized at this meeting for all participants. Written informed consent must be provided before any potential participant is allowed to participate. Consent will not be required prior to eligibility screening.

For adolescents aged 16-17 years, we will obtain both informed assent from the adolescent and written informed consent from the adolescent's guardian. When explaining the risks involved in participation to adolescents, we will be very clear what study participation entails to help adolescents make an informed decision regarding study participation (as explained above in the section on risks). During the consent

process, study staff will answer all questions clearly and with patience, recognizing that additional information and time for a decision may be needed regarding potential adolescent participants. A separate informed assent form will be provided for the adolescents along with an informed consent form for their guardians. No special procedures will be followed for pregnant adolescents. As explained in the section on risks (vulnerable subjects), pregnant women and their unborn babies will be at no increased risk through study participation. The study will not impact on the choice of ART made for the pregnant women. The same is true for pregnant adolescents.

Staff will be offered the ICF to read (and take home, if desired) and a private place to review study participation and the consent process with a study staff member before signing. To limit any pressure or possibility of coercion to participate, they will be reminded that participation is voluntary and that no one will reveal to others whether or not they participated. The survey and/or IDI will be held in a private place and time preferred by the staff member to protect their privacy regarding participation (or lack of participation).

For study staff: The DTHF employee who will recruit study staff will also conduct the short surveys and interviews. Again, she will stress that participation is voluntary during the consent process to help minimize the risk of coercion to participate.

A similar process will be undertaken with regard to stakeholders.

Residents in Cape Town usually speak English or Xhosa, so potential participants will likely include individuals who are fluent in one or both of these languages. After our English language consent forms are approved by the UCT REC and BUMC IRB, they will be translated into Xhosa, for use with potential participants whose primary language is Xhosa. We will thus be able to use a consent form in whichever language the potential participant is most comfortable. Our local research staff can speak and read both languages so using these forms will be feasible for them. Subjects will be given a copy of the consent form if they wish to receive one. For limited/non-readers, a witness who is not a member of the study team will be present.

Signed informed consent forms will be kept with the study team and returned to our offices where they will be stored in a locked restricted access cupboard.

While a device (EAM) will be used in this study, it is a monitoring device only and has been used by the local study team in numerous previous studies in an appropriate and acceptable fashion. Thus we are confident that trained and experienced study staff will be able to describe the study and review consent with potential participants.

These consent procedures are standard for these types of studies in Cape Town. Our study staff is experienced with this type of research and are comfortable with the measures described here.

J4. Non-English consent forms

We will obtain consent from subjects who are not fluent in English by use of local-language consent forms. After our English language consent forms are approved by the UCT REC and BUMC IRB, they will be translated into isiXhosa, for use with potential participants whose primary language is one of those languages. We will thus be able to use a consent form in whichever language the potential participant is

most comfortable. Our local research staff can speak and read these languages so using these forms will be feasible for them.

PART K. Data Handling and Record Keeping

K1. Confidentiality

To protect the privacy of participants and potential participants, we confirm that:

a) The information that will be obtained from and/or about participants and potential participants is the minimum necessary to conduct the study; and
b) If any interventions and interactions occur with participants and potential participants, they will take place in private settings.

K2. Access to Data

All subjects will be assigned and identified by a unique ID number, as will their parent/guardian, whose ID number will be associated with the adolescent for whom they provide care. Subject names will not be entered into any analytic databases. A single master log sheet linking patient names to unique numbers, together with the locator files that contain name and contact information, will be kept under strict lock and key at each study site. These will be destroyed (by shredding) after the study and follow-up is complete. The study number alone will identify all forms containing the results of adherence monitoring, clinical examinations, laboratory tests, questionnaires, or data related to the IDIs and FGD.

After data collection is completed, we will ensure participant confidentiality and privacy during this study to the greatest degree possible. All study data, including the audio-recordings, will be kept in locked cabinets in locked offices to avoid inadvertent disclosure of identity or private information. Study participants will not be identified by name nor have their answers linked to any personal identifying information in written records. The names and contact information collected at the beginning of the study will be destroyed at the end of the study. All study analyses presented in technical reports, manuscripts, and articles will be presented in aggregate form, with no individual identifying information.

Only the DTHF PI and study staff (all of whom are based in South Africa) will have access to these data. BU staff will not have access to these original research data. Digital audio recordings will be immediately (same day) transferred to an encrypted hard drive and deleted from the recording device. The DTHF researchers will transcribe the audio-recordings from the encrypted hard drives (omitting any names, if they happen to be recorded by mistake). Redacted transcriptions will be send to BU.

Other written data, including ICFs, will be kept in a locked drawer/cupboard and/or on a password-protected computer in a locked office at BU and DTHF. All data will be retained for at least 7 years after the end of the study. At that time, all study data will be destroyed. The audio-tapes of the IDIs and FGDs will be destroyed by DTHF staff at that time as well.

Regarding the study staff who participate in Aim 2 IDIs and short surveys: While the RAs have access to the REDCap database for Aim 1, they will not have access to the secure hard drive where all IDI recordings and transcripts (for Aim 1 and Aim 2) will be kept. The transcription and translation will also be done by an external group, and not internally. For the short survey data, these data will be collected

on hard copy (not via REDCap) and data clerks at the DTHF will input data from the hard copy CFFs into Excel (with only an ID#, and no identifying information). The Excel file will be kept on the same secure hard drive as the qualitative recordings and translated documents, to which the RAs will not have access.

K3. Source documents

All data will be collected according to the data collection plan described in section E2 (Data Collection) above. Here we list the source documents for data collection related to human subjects (all are included in the appendix).

1. Screening Form (SC001)
2. Eligibility and Enrollment Form (EL001)
3. Locator Form (AD001)
4. Baseline Demographics (EL001a)
5. Baseline Medical History (DM002)
6. Wisepill Status (WP001)
7. Randomisation Form (RN001)
8. Annual Questionnaire (AQ001)
9. Patient Serial IDI Guide (SI001)
10. Brief Questionnaire for Participants (BQ001)
11. Brief Questionnaire for Clinic and Study Staff (BQ002)
12. IDI Guide for Patients (Aim 2) (PI001)
13. IDI Guide for Clinic and Study Staff (Aim 2) PI002)
14. Time and Motion Study Form (Aim 2) (TM001)
15. FGD Guide for Policy-makers (Aim 2)(PM001)

K4. Retention of Study Data

All data will be retained for at least 7 years after the end of the study (Q1 or year 5). At that time, all study data will be destroyed.

PART L: HIPAA Compliance

N/A. We do not need access to protected health information without signed authorization from the individual whose information we need.

PART M: Cost / Payment

There are no costs associated with participation in the study above and beyond the time required to participate in various activities (explained above in procedures). As is typical in research of this kind in South Africa, we will compensate participants for their time and engagement in the study. At each study visit that requires procedures or data collection above and beyond the standard of care, we will provide each participant with R150 (≈US$8) e.g., viral load test, questionnaire, or IDI. Activities for all trial

participants will take place at M0, M12*, M12, M18, M24. Thus participants who complete the study will receive R750 (≈US$40). Those who participate in either the serial IDIs (Aim 1) or the IDIs for Aim 2 would receive an extra R150 (≈US$8) for each IDI. Thus the maximum a participant might receive is R1200 (≈US$64), for standard activities plus 3 serial IDIs (maximum possible) over 24 months of participation. (Participants chosen for the Aim 1 IDIs will not be selected for the Aim 2 IDIs.)

There will be no compensation provided to clinic staff, study staff, or policy-makers who participate in a questionnaire, IDI, or FGD, though drinks and snacks may be provided.

PART N: Study Timeline

Description of timeline

As shown in the Study Timeline (Table 4), Aim 1 activities will be implemented beginning mid-way in Year 1 to mid-way in Year 4 of the study, following 6 months of final study and site preparation. We anticipate recruiting our first subject in month 7 of Year 1 which would be in March of 2022, if the study is able to begin on Sept 1, 2021. We have planned for 21 months of recruitment, followed by 24 months of follow-up. In the final 15 months of the study, we will complete the analyses required in Aims 2 and 3: namely cost analyses and determination of key implementation features; as well as using modelling to determine the most cost-effective and scalable combination of study components. In Year 4, we anticipate being able to share initial results (relating to implementation, detection of nonadherence, etc.) at conferences and in manuscripts. In Year 5, we will complete all main analyses and engage in preparation of abstracts, more manuscripts, and additional in-country dissemination activities. As detailed in our budget narrative, we also plan to hold an intensive data analysis workshop in Year 5 in Boston, to which several collaborators from Cape Town will travel to engage with the Boston-based team on analyses and manuscript-drafting.

Table 4. Study Timeline

(year 1 begins at date of study award, anticipated September 2021):

Aim	Activity	Year 1				Year 2				Year 3				Year 4				Year 5			
		Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
1	Prepare for SUSTAIN study	X	X																		
1	Protocol completion	X																			
1	Ethics approvals	X																			
1	Final approval from COCT clinics		X																		
1	Staff training		X																		
1	Eligibility			X	X	X	X	X	X												
1	Enrollment			X	X	X	X	X	X	X											
1	Follow-up			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
1	Adherence intervention (if nonadherence detected)			X	X	X	X	X	X	X	X	X	X	X	X	X					

2,3	Collect implementation data (and conduct FGD with COCT officials)				X	X	X	X	X	X	X	X	X	X	X	X	X	X		
1,2	Data cleaning				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
1,2	Analyze effectiveness (Aim 1) and cost and key implementation features (Aim 2)														X	X	X	X	X	
3	Optimization through statistical modelling																	X	X	X
1,2, 3	Data analysis workshop																	X		
1,2, 3	Manuscript writing and submission														X	X	X	X	X	X
1,2, 3	Dissemination of findings														X	X	X	X	X	X

PART O: Biological Samples

Blood will be drawn from trial participants for HIV viral load testing. As explained in the data collection section, two additional blood draws will be conducted for viral load testing above and beyond standard of care. They will take place at Months 0 and 18. Additional data will be collected at Month 0 (enrollment) via a questionnaire, but the Month 18 blood draw will be the only data collected at that time beyond any necessary updating of contact information. At each blood draw, 5mL will be drawn, with testing performed using nationwide approved procedures at the National Health Laboratory Systems (NHLS) in Cape Town. A total of 10mL will be drawn from each participant across the life of the study.

The samples will not be stripped of identifiers, as the results of each test will be placed in the subject's medical chart. However, for study purposes, all HIV viral load test results will be collected and identified by a study ID number only.

No samples will be released to anyone outside of the study sites in Cape Town, South Africa, or sold to anyone.

If a subject withdraws from the study, the blood samples themselves will be handled per standard procedures at the NHLS in Cape Town as with all subjects, which means they will be discarded after test results are documented in their medical chart. For study purposes, the results of the viral load testing will be retained for use in analyses unless the participant revokes permission to use test results.

PART P: Device Use

As explained in the study description, this study will make use of pill containers that have the capacity to

monitor openings via wireless technology. The containers have a SIM card that can transmit data on container openings by general packet radio service (GPRS) to an off-site web-based server and/or by short message service (SMS). The devices transmit data, but perform no direct therapeutic function, do not enter a patient's body, and are not drugs. They pose no physical harm or risk to users. The company that makes the device (Wisepill Technologies) wrote us that FDA approval is not required for Wisepill because it is neither a medication nor comes into contact with a medication, and is only a vial closure, not a "medical device". As the device is not being used as a medical intervention, we do not believe that a waiver of Investigational Device Exemption is required in this context. For comparison and guidance, please refer to BUMC IRB approved protocols #H-30374 and #H32876, which made use of the same EAM device.

P1. Plans for control and use of the device.

The devices will be stored in the local PI's research offices where access is limited to study staff. When a participant is enrolled, he/she will be shown how to store medications in the device and how to open and close it. Participants will be instructed to contact study staff or return to a study site if there are any issues with the device, which is only used for storing medications by the participant. At each study visit, the participant will show study staff the device and will be asked whether there are any issues with its use. In many previous studies using this device, both at the local site and elsewhere, we have not experienced any problem with device use.

A pdf of the Wisepill RT 2000 medication dispenser from the Wisepill Technologies website was attached to the protocol for the BUMC IRB.

Further information on Wisepill may be found on the Wisepill Technologies website:
https://www.wisepill.com/

References

1. Katz IT, Kaplan R, Fitzmaurice G, Leone D, Bangsberg DR, Bekker LG, Orrell C. Treatment guidelines and early loss from care for people living with HIV in Cape Town, South Africa: A retrospective cohort study. *PLoS Med.* Nov 2017; **14**(11): e1002434.
2. Orrell C, Cohen K, Leisegang R, Bangsberg DR, Wood R, Maartens G. Comparison of six methods to estimate adherence in an ART-naive cohort in a resource-poor setting: which best predicts virological and resistance outcomes? *AIDS Res Ther.* Apr 4 2017; **14**(1): 20.
3. Orrell C, Cohen K, Mauff K, Bangsberg DR, Maartens G, Wood R. A Randomized Controlled Trial of Real-Time Electronic Adherence Monitoring With Text Message Dosing Reminders in People Starting First-Line Antiretroviral Therapy. *J Acquir Immune Defic Syndr.* Dec 15 2015; **70**(5): 495-502.
4. Haberer JE, Bwana BM, Orrell C, Asiimwe S, Amanyire G, Musinguzi N, et al. ART adherence and viral suppression are high among most non-pregnant individuals with early-stage, asymptomatic HIV infection: an observational study from Uganda and South Africa. *J Int AIDS Soc.* Feb 2019; **22**(2): e25232.
5. El-Khatib Z, Ekstrom AM, Coovadia A, Abrams EJ, Petzold M, Katzenstein D, Morris L, Kuhn L. Adherence and virologic suppression during the first 24 weeks on antiretroviral therapy among women in Johannesburg, South Africa - a prospective cohort study. *BMC Public Health.* Feb 8 2011; **11**: 88.
6. Haberer JE, Bwana BM, Orrell C, Asiimwe S, Amanyire G, Musinguzi N, Siedner MJ, Bell K, Kembabazi A, Mugisha S, Kibirige V, Cross A, Kelly N, Bangsberg D. Adherence in early versus late ART initiation in sub-Saharan Africa. Conference of Retrovirus and Opportunistic Infection (CROI); February 2018. Boston, MA.
7. Steegen K, Carmona S, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D, MacLeod W, Sanne I, Stevens WS. Moderate Levels of Pre-Treatment HIV-1 Antiretroviral Drug Resistance Detected in the First South African National Survey. *PLoS One.* 2016; **11**(12): e0166305.
8. Takuva S, Brown AE, Pillay Y, Delpech V, Puren AJ. The continuum of HIV care in South Africa: implications for achieving the second and third UNAIDS 90-90-90 targets. *AIDS.* Feb 20 2017; **31**(4): 545-52.
9. Mabunda K, Ngamasana EL, Babalola JO, Zunza M, Nyasulu P. Determinants of poor adherence to antiretroviral treatment using a combined effect of age and education among human immunodeficiency virus infected young adults attending care at Letaba Hospital HIV Clinic, Limpopo Province, South Africa. *Pan Afr Med J.* 2019; **32**: 37.
10. UNAIDS. UNAIDS Data: 2017. 2017. Available at: http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf (accessed April 22 2019).
11. World Health Organization, Regional Office for Africa. End HIV/AIDS by 2030. HIV/AIDS: Framework for Action in the WHO Africa Region, 2016-2020, 2017. Available at: https://apps.who.int/iris/bitstream/handle/10665/259638/EndAIDS-eng.pdf;jsessionid=AE96079039DB8485094EF95E0A70B2A6?sequence=1
12. Ncaca LN, Kranzer K, Orrell C. Treatment interruption and variation in tablet taking behaviour result in viral failure: a case-control study from Cape Town, South Africa. *PLoS One.* 2011; **6**(8): e23088.
13. Parienti JJ, Barrail-Tran A, Duval X, Nembot G, Descamps D, Vigan M, Vrijens B, Panhard X, Taburet AM, Mentre F, Goujard C. Adherence profiles and therapeutic responses of treatment-naive HIV-infected patients starting boosted atazanavir-based therapy in the ANRS 134-COPHAR 3 trial. *Antimicrob Agents Chemother.* May 2013; **57**(5): 2265-71.
14. Parienti JJ, Das-Douglas M, 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.

15. Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG. Risk factors associated with default among new smear positive TB patients treated under DOTS in India. *PLoS One.* 2010; **5**(4): e10043.
16. Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, Eusuff SI, Sadacharam K, Narayanan PR. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. *Int J Tuberc Lung Dis.* May 2005; **9**(5): 556-61.
17. Cadosch D, Abel Zur Wiesch P, Kouyos R, Bonhoeffer S. The Role of Adherence and Retreatment in De Novo Emergence of MDR-TB. *PLoS Comput Biol.* Mar 2016; **12**(3): e1004749.
18. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ.* May 17 2008; **336**(7653): 1114-7.
19. Hiligsmann M, Cornelissen D, Vrijens B, Abrahamsen B, Al-Daghri N, Biver E, et al. Determinants, consequences and potential solutions to poor adherence to anti-osteoporosis treatment: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF). *Osteoporos Int.* Nov 2019; **30**(11): 2155-65.
20. Orrell C, Kaplan R, Wood R, Bekker LG. Virological breakthrough: a risk factor for loss to followup in a large community-based cohort on antiretroviral therapy. *AIDS Res Treat.* 2011; **2011**: 469127.
21. Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG, Wood R. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. *Antivir Ther.* 2007; **12**(1): 83-8.
22. Liu H, Golin CE, Miller LG, Hays RD, Beck CK, Sanandaji S, Christian J, Maldonado T, Duran D, Kaplan AH, Wenger NS. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med.* May 15 2001; **134**(10): 968-77.
23. Gill CJ, Sabin LL, Hamer DH, Keyi X, Jianbo Z, Li T, Wu WJ, Wilson IB, Desilva MB. Importance of dose timing to achieving undetectable viral loads. *AIDS Behav.* Aug 2010; **14**(4): 785-93.
24. Haberer J. Real-Time HIV Antiretroviral Therapy Adherence Monitoring in a Resource-Limited Setting. *Annals of Behavioral Medicine.* Apr 2011; **41**: S143-S.
25. Haberer JE, Kiwanuka J, Nansera D, Muzoora C, Hunt PW, So J, O'Donnell M, Siedner M, Martin JN, Bangsberg DR. Realtime adherence monitoring of antiretroviral therapy among HIV-infected adults and children in rural Uganda. *AIDS.* Aug 24 2013; **27**(13): 2166-8.
26. Haberer JE, Musiimenta A, Atukunda EC, Musinguzi N, Wyatt MA, Ware NC, Bangsberg DR. Short message service (SMS) reminders and real-time adherence monitoring improve antiretroviral therapy adherence in rural Uganda. *AIDS.* May 15 2016; **30**(8): 1295-300.
27. Haberer JE, Musinguzi N, Tsai AC, Boum Y, 2nd, Bwana BM, Muzoora C, Hunt PW, Martin JN, Bangsberg DR. Real-time electronic adherence monitoring plus follow-up improves adherence compared with standard electronic adherence monitoring. *AIDS.* Jan 2 2017; **31**(1): 169-71.
28. Haberer JE, Robbins GK, Ybarra M, Monk A, Ragland K, Weiser SD, Johnson MO, Bangsberg DR. Real-time electronic adherence monitoring is feasible, comparable to unannounced pill counts, and acceptable. *AIDS Behav.* Feb 2012; **16**(2): 375-82.
29. Bachman DeSilva M, Gifford AL, Keyi X, Zhong L, Feng C, Brooks M, Harrold M, Yueying H, Gill CJ, Wubin X, Vian T, Haberer J, Bangsberg D, Sabin L. Feasibility and Acceptability of a Real-Time Adherence Device among HIV-Positive IDU Patients in China. *AIDS Res Treat.* 2013; **2013**: 957862.
30. Bachman DeSilva M, Gifford AL, Bonawitz R, Zhong L, F. Z, Mu W, Li Y, Zeng X, CJ G, Sabin L. Real time electronic drug monitoring (EDM) for HIV-positive adolescents: promising acceptability and feasibility in China. *Journal of AIDS & clinical research.* 2016; **7:586. doi: 10.4172/2155-6113.1000586.**(586).
31. World Health Organization. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. Geneva, 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf?sequence=1

32. Research team. TB MONITORING ADHERENCE AND TREATMENT ENDPOINTS PROJECT. 2019. Available at: https://pactr.samrc.ac.za/Search.aspx (accessed Nov 18 2020).
33. Subbaraman R, de Mondesert L, Musiimenta A, Pai M, Mayer KH, Thomas BE, Haberer J. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. *BMJ Glob Health.* 2018; **3**(5): e001018.
34. Stop TB Partnership. Smart medication container included in Stop TB Partnership's Global Drug Facility product catalog. 2020. Available at: http://www.stoptb.org/news/stories/2020/ns20_031.html.
35. Orrell C, Dipenaar R, Killa N, Tassie JM, Harries AD, Wood R. Simplifying HIV cohort monitoring--pharmacy stock records minimize resources necessary to determine retention in care. *Journal of acquired immune deficiency syndromes (1999).* Mar 1 2013; **62**(3): e106-8.
36. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA : the journal of the American Medical Association.* Jul 25 2012; **308**(4): 387-402.
37. Puttkammer N, Zeliadt S, Balan JG, Baseman J, Destine R, Domercant JW, France G, Hyppolite N, Pelletier V, Raphael NA, Sherr K, Yuhas K, Barnhart S. Development of an electronic medical record based alert for risk of HIV treatment failure in a low-resource setting. *PLoS One.* 2014; **9**(11): e112261.
38. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: A systematic review and meta-analysis. *PLoS One.* 2018; **13**(9): e0204091.
39. Medecins Sans Frontieres Khayelitsha. SUPPORTING ADHERENCE TO ANTIRETROVIRAL TREATMENT: A FACILITY APPROACH TO REDUCE THE RISK OF TREATMENT FAILURE: REPORT AND TOOLKIT. Available at: https://www.msf.org.za/system/tdf/risk_of_treatment_failure_mentorship_toolkit_v3.pdf?file=1&type=node&id=3080
40. Dr. Beth Harley, Clinical Medical Officer, City of Cape Town. Personal communication to Dr. Catherine Orrell. November 19, 2019.
41. Wisepill Technologies. Wisepill Tecnologies home page. Available at: https://www.wisepill.com/ (accessed July 18 2018).
42. Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JI, Thorlund K, Nachega JB, Mills EJ. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV.* Jan 2017; **4**(1): e31-e40.
43. Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S. Packaging interventions to increase medication adherence: systematic review and meta-analysis. *Curr Med Res Opin.* Jan 2015; **31**(1): 145-60.
44. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, Griffey R, Hensley M. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health.* Mar 2011; **38**(2): 65-76.
45. Pyne JM, Asch SM, Lincourt K, Kilbourne AM, Bowman C, Atkinson H, Gifford A. Quality indicators for depression care in HIV patients. *AIDS Care.* Oct 2008; **20**(9): 1075-83.
46. Kanwal F, Pyne JM, Tavakoli-Tabasi S, Nicholson S, Dieckgraefe B, Storay E, Bidwell Goetz M, Smith DL, Sansgiry S, Gifford A, Asch SM. Collaborative Care for Depression in Chronic Hepatitis C Clinics. *Psychiatr Serv.* Oct 1 2016; **67**(10): 1076-82.
47. Pyne JM, Fortney JC, Curran GM, Tripathi S, Atkinson JH, Kilbourne AM, Hagedorn HJ, Rimland D, Rodriguez-Barradas MC, Monson T, Bottonari KA, Asch SM, Gifford AL. Effectiveness of collaborative care for depression in human immunodeficiency virus clinics. *Arch Intern Med.* Jan 10 2011; **171**(1): 23-31.
48. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, Boynton MH, Halko H. Psychometric assessment of three newly developed implementation outcome measures. *Implement Sci.* Aug 29 2017; **12**(1): 108.

49. Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. *Lancet Glob Health.* Jan 2014; **2**(1): e23-34.
50. Wouters E, Heunis C, van Rensburg D, Meulemans H. Patient satisfaction with antiretroviral services at primary health-care facilities in the Free State, South Africa--a two-year study using four waves of cross-sectional data. *BMC Health Serv Res.* Oct 9 2008; **8**: 210.
51. http://www.ssi.dk/sw378.asp. Statens Serums Institute.
52. Chaiyachati KH, Ogbuoji O, Price M, Suthar AB, Negussie EK, Barnighausen T. Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. *AIDS.* Mar 2014; **28 Suppl 2**: S187-204.
53. Gross R, Zheng L, La Rosa A, Sun X, Rosenkranz SL, Cardoso SW, et al. Partner-Focused Adherence Intervention for Second-line Antiretroviral Therapy: A Multinational Randomized Trial (ACTG A5234). *The lancet HIV.* Jan 1 2015; **2**(1): e12-e9.
54. Demena BA, Artavia-Mora L, Ouedraogo D, Thiombiano BA, Wagner N. A Systematic Review of Mobile Phone Interventions (SMS/IVR/Calls) to Improve Adherence and Retention to Antiretroviral Treatment in Low-and Middle-Income Countries. *AIDS Patient Care STDS.* Feb 2020; **34**(2): 59-71.
55. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach (2nd ed.). New York: Guilford Press; 2017.
56. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods.* Jun 2013; **18**(2): 137-50.
57. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods.* Dec 2010; **15**(4): 309-34.