Project Title: **Hybrid Effectiveness-Implementation Trial for ART Adherence and Substance Use in HIV Care in South Africa**

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PROJECT SUMMARY

Background: South Africa has the highest number of HIV-infected individuals in the world (approximately 7 million), and increasing numbers of patients are initiating antiretroviral therapy (ART), leading to greater risk of ART nonadherence and HIV transmission. Alongside the HIV/AIDS epidemic, there has been an alarming increase in substance use in South Africa, particularly in the Western Cape. South Africa also has one of the highest per capita global rates of alcohol consumption. Despite the impact of untreated substance use on poor HIV treatment outcomes and continued HIV transmission, there is little integration of substance use treatment into HIV care in this area.

Preliminary Work: In the first phase of this trial (HREC ref: 210/2015), semi-structured interviews were conducted to identify key barriers and facilitators in implementing an evidence-based intervention for ART adherence and substance use in this setting (*n*=30). Findings from these interviews were used to guide the treatment adaptation and implementation strategy for the present study.

Design: This next phase of this study is a randomized, hybrid effectiveness-implementation trial designed to assess the feasibility, acceptability, and effectiveness of a paraprofessional-delivered intervention for ART adherence and substance use in HIV care in South Africa. The adapted, integrated care model will be compared to an enhanced standard of care in this setting. To provide care for those most in need, participants will be patients with HIV who are struggling with ART adherence and have elevated substance use risk (indicated by the WHO-Assist). Primary outcomes include adherence to ART, substance use, and acceptability/feasibility of the intervention.

SPECIFIC AIMS

South Africa (SA) is home to the largest number of HIV-infected individuals in the world (6.8 million).[1] As increasing numbers of patients are initiating antiretroviral therapy (ART) in SA, there is greater risk of ART nonadherence and failure of the only available first and second line ART regimens.[2,3] Given recent evidence of higher likelihood of HIV transmission with detectable virus, nonadherence may also increase HIV transmission.[4]

Alongside the HIV/AIDS epidemic, there has been an alarming increase in substance use in SA, particularly in Western Cape.[1,5] In Cape Town, there have been drastic increases in the use of methamphetamine ("tik"). Only 0.3% of patients in substance use treatment in Cape Town in 2002 used tik, whereas this was estimated to be 50% by 2012.[5] South Africa also has one of the highest global rates of per capita alcohol consumption.[6]

In SA, substance use is largely not addressed in HIV care. This is a "missed opportunity" for maximizing HIV treatment outcomes, as substance use is prevalent among HIV-infected individuals in SA—with an estimated 13-37% of patients in HIV clinics presenting with substance use[7]—and when untreated, associated with worse ART adherence, greater likelihood of failing the available first- and second-line ART regimens, lower rates of viral suppression, and greater likelihood of HIV transmission.[7-10]

The success of treatment as prevention (TasP) relies on the implementation of evidence-based interventions to address substance abuse and ART adherence. Evidence-based interventions exist to address ART adherence, such as problem solving therapy.[11-13] Developed initially in high-income settings, problem solving has accumulated empirical support to address ART adherence in resource-limited settings, including sub-Saharan Africa.[14,15] Problem solving therapy also has accumulating support to reduce substance use in South Africa, particularly when combined with other brief interventions, such as behavioral activation[16,17] and motivational interviewing.[18,19] Yet, there is a gap between efficacy research and actual implementation of these evidence-based interventions in HIV care in SA.

Sustainable and scalable implementation will require task shifting/sharing with paraprofessionals. SA has a shortage of trained health care workers to address the growing HIV epidemic, making task shifting/sharing with paraprofessionals, such as lay adherence or peer counselors, essential.[20] Problem solving, behavioral activation, and motivational interviewing have been delivered by lay counselors in sub-Saharan Africa to separately address substance use[18,19,21] and ART nonadherence.[18,19,21,22] Yet, there is less empirical support evaluating the effectiveness and implementation of a paraprofessional-delivered, integrated intervention to address both substance use and ART adherence in HIV care.

Important implementation questions remain before an integrated, paraprofessional-delivered intervention could be rolled out in HIV care, which could be addressed in a Type I hybrid effectiveness-implementation trial.[23] This design assesses the effectiveness of an intervention in a new setting, while also collecting pilot implementation outcomes on feasibility, acceptability, and barriers/facilitators to implementation).

The current study proposes a hybrid effectiveness-implementation design to evaluate an evidence-based, paraprofessional-delivered intervention for ART adherence and substance use (compared to standard of care). Aims follow a well-established implementation model (RE-AIM[24]; see Figure 1, p.8). **The overall aim is to** evaluate an adapted, paraprofessional-delivered intervention in a randomized, hybrid effectiveness-implementation design[1] (*n*=60; compared to standard of care) on the following:

a) Effectiveness: Primary: (1) ART adherence (measured using real-time wireless electronic adherence monitoring); (2) Substance use (urinalysis and self-report); Exploratory: (3) viral suppression

b) Implementation: Feasibility and acceptability: (1) Provider fidelity to intervention delivery; (2) Patient participation and retention; and (3) Qualitative perceptions on feasibility, acceptability, and barriers and facilitators to implementation.

BACKGROUND AND SIGNIFICANCE

A. SIGNIFICANCE

South Africa (SA) is home to the largest number of HIV-infected individuals in the world (6.8 million).[1] HIV/AIDS is the leading cause of life years lost in South Africa and disproportionately affects individuals living in peri-urban areas. The country has a large antiretroviral therapy (ART) program, but some individuals exhibit poor ART adherence, which increases the likelihood of developing drug resistance and failing the only available first and second line ART regimens in South Africa.[2,3] Given recent evidence of higher likelihood of HIV transmission with detectable virus, nonadherence may also increase HIV transmission.[4]

Alongside the HIV/AIDS epidemic, there has been an alarming increase in substance use in SA, particularly in Western Cape.[1,5] In Cape Town, the largest city in the Western Cape, there have been drastic increases in the use of methamphetamine ("tik"). Only 0.3% of patients in substance use treatment in Cape Town in 2002 used tik, whereas this was estimated to be 50% by 2012.[5] South Africa also has one of the highest global rates of per capita alcohol consumption.[6] An estimated 13-37% of HIV clinic-attending patients in peri-urban areas of Cape Town present with substance use,[7] which is concerning as untreated substance use is associated with worse ART adherence, lower rates of viral suppression, and HIV transmission risk.[7–10]

In South Africa, substance use is largely not addressed in HIV care. Despite the impact of untreated substance use on poor HIV treatment outcomes and continued HIV transmission, there is little if any integration of substance use treatment into HIV care in South Africa,[24] which creates a fragmented and incomplete system of care.[25] This is a "missed opportunity" for maximizing HIV treatment outcomes, as substance use is prevalent among HIV-infected individuals in South Africa, with an estimated 13-37% of patients in HIV clinics presenting with substance use.[7,8] Furthermore, when untreated, substance use is associated with worse ART adherence, greater likelihood of failing the available first- and second-line ART regimens, lower rates of viral suppression, and greater likelihood of HIV transmission.[1,7–10] This lack of integration is also present despite evidence that lay adherence counselors have been shown to reliably screen for substance use in HIV clinic settings.[26,27] Implementing evidence-based screening and treatment to address substance use and ART adherence in HIV care in the Western Cape may maximize effectiveness of HIV treatment and reduce the likelihood of HIV transmission in this population.

The success of treatment as prevention (TasP) relies on the implementation of evidence-based interventions to address substance use and ART adherence. Evidence-based interventions to address ART adherence and substance use exist and have accumulated support in resource-limited settings. Although first developed and tested in the U.S., problem-solving based interventions to improve ART adherence[11-13] have empirical support in resource-limited settings, including sub-Saharan Africa. Additionally, when combined with other brief interventions such as behavioral activation (BA) and motivational interviewing (MI), problem-solving therapy also has empirical support for reducing alcohol and other substance use,[16,17,28-32] including evidence specifically in South Africa.[18,19,21] However, to date, there has been minimal research to evaluate an integrated intervention using problem solving, BA, and MI to address ART adherence and substance use in HIV care.

Sustainable and scalable implementation will require task shifting/sharing with paraprofessional providers. Given that South Africa has the highest burden of HIV/AIDS, yet a shortage of trained health care workers to address the growing epidemic, task shifting/sharing (i.e. shifting/sharing health service responsibilities with lower cadres of health workers[20]) is essential for a treatment model to be sustainable and scalable in this setting. In South Africa, "lay counselors" deliver adherence counseling in public HIV clinics. While lay counselors typically have a high school education or less and do not have formal professional training, prior

studies have shown that problem solving, BA, and MI can be feasibly and effectively delivered by lay counselors (e.g., in Kenya[33] and South Africa[18,19,21,22]).

B. INNOVATION

The present study seeks to identify methods to integrate substance use screening and treatment into HIV care. It addresses a key research priority put forth by the South African Medical Research Council (MRC) and the World Health Organization (i.e., examining the integration of substance use interventions in HIV care settings and evaluating the impact on HIV and substance use outcomes).[24]

The study proposes a hybrid effectiveness-implementation design, which aims to simultaneously collect data on effectiveness of an intervention in a new setting while also collecting important data on implementation. This hybrid approach is meant to speed the translation of knowledge from efficacy trials to actual implementation. Although this is a recommended approach in the implementation science field, to date, efforts to apply this model have largely been focused on domestically in the VA system.[23] This study would extend the use of the hybrid effectiveness-implementation design to a resource-limited global setting in order to speed the translation of knowledge into the clinical setting.

The present study also evaluates a collaborative care model for the integration of HIV and substance use services, and substance use screening and treatment into primary care.[34] This study lays the framework for supporting the development of innovative and collaborative care models in the US in the future.

Additionally, individuals who have failed first-line ART are at risk for ongoing nonadherence because they did not achieve viral suppression with first line agents. By selecting these multiply challenged patients from the clinics, the potential impact of the intervention is maximized in that, if successful, it will minimize the chances that these patients will need third-line treatment, not currently available in public SA clinics. The long-term success of TasP relies on addressing substance use and ART adherence.

Finally, the use of real-time wireless electronic adherence monitoring technology is an innovative strategy for real-time assessment of our primary outcome, ART adherence. This study will provide important pilot data on the acceptability and feasibility of real-time wireless monitoring among HIV-infected substance users in sub-Saharan Africa.

C. PRELIMINARY STUDIES

Paraprofessional counsellors can reliably screen for substance use in Cape Town. Dr. Magidson recently collaborated with co-mentors Drs. Joska and Myers to document the feasibility of lay counselor screening for substance use using the WHO-ASSIST, the proposed screening tool in this study for patients presenting to a co-located substance use/HIV treatment setting.[35,36] Additionally, in other studies, co-mentor Dr. Joska has shown that lay counselors can reliably screen for and detect substance use in HIV care in South Africa with good sensitivity (94%) and specificity (85%).[26,27]

Paraprofessional counsellors can be trained in and deliver problem solving and behavioral activation-based interventions in sub-Saharan Africa. Dr. Myers, K co-mentor, has led a series of studies in South Africa showing the feasibility of training peer counselors to deliver problem solving, MI, and behavioral activation. Additionally, these studies have shown significant reductions in substance use at a three month follow up.[18,19,21] Dr. Magidson and Dr. O'Cleirigh co-trained five lay counselors in Zimbabwe in a problem solving intervention for adherence, which was found to be feasible and acceptable.[37,38] Other work led by Drs. Joska, Andersen, and Safren has demonstrated the feasibility and acceptability of a nurse-delivered problem solving intervention for adherence, which was associated with increases in ART adherence over 3 months (p=.01), and >90% retention.[39]

There is evidence that problem solving for ART adherence may need tailoring for

substance users. Prior studies by co-mentor Dr. Safren have shown that maintenance of adherence gains following a problem solving intervention for ART adherence is compromised by substance use relapse.[40,41] This suggests that an intervention not specifically tailored for substance users may not be effective alone to improve ART adherence, and that ART nonadherence and substance use should be addressed simultaneously.

Real-time wireless electronic adherence monitoring (EAM) is feasible and acceptable for assessing ART adherence in a resource-limited setting in sub-Saharan Africa. Prior work has shown the feasibility and acceptability of using Wisepill, a wireless EAM device to assess real-time ART adherence among HIV clinic attendees in Uganda[10] and among HIV-infected substance users in China.[42] Drs. Joska and Andersen also have used Wisepill as a feasible assessment of ART adherence in South Africa.[39]

Qualitative data to inform intervention. In Phase 1 of this study, individual semi-structured interviews (*n*=30) were conducted to identify key barriers and facilitators to implementing an evidence-based intervention for ART adherence and substance use in this setting. The findings from these interviews were used to guide the treatment adaptation and implementation strategy for the present study. The interviews focused on (1) the appropriateness of existing evidence-based interventions for adherence and substance use for the SA HIV clinic setting; (2) cultural and linguistic considerations for the behavioral intervention adaptation; (3) identifying who may be most appropriate to deliver the intervention and adaptations for paraprofessional delivery; (4) feasibility and appropriateness of focusing on substance use more broadly rather than a single substance; and (5) identifying barriers and facilitators to implementation of the intervention in this setting.[43]

Based on the findings from the qualitative analysis in Phase 1, in addition to a review of behavioral intervention components that are (1) empirically supported for both ART adherence and substance use; (2) have been evaluated in SA; and (3) feasibly delivered by paraprofessional counsellors [18,19,21,22,44], the treatment was adapted for the present study for paraprofessional delivery. Adaptations to content were suggested, including focusing on myths associated with mixing ART and substance use, identifying specific substance free enjoyable activities that are feasible and acceptable in the community, identifying healthy coping strategies for psychological distress, cravings, and high risk situations for substance use, and the role of HIV and substance use stigma as potential barriers to integration in this setting.

METHODS

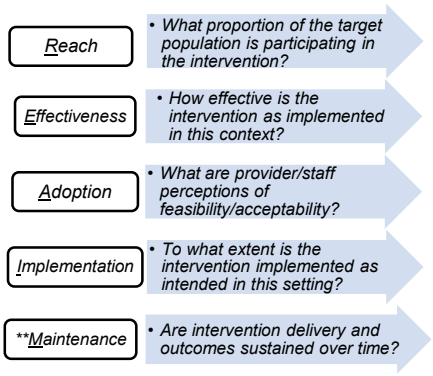
A. Approach

Overview. The goal of this study is to optimally adapt and implement an integrated intervention for ART adherence and substance use in the HIV care setting in South Africa *(n*= 60). The integrated intervention is specifically designed to be implemented by non-specialist counsellors in local HIV clinics to support sustainability and facilitate dissemination. Based on our qualitative work, a randomized, Type I hybrid effectiveness-implementation design will be conducted to assess the effectiveness, feasibility and acceptability of the intervention.

Conceptual Framework. A Type 1 hybrid effectiveness-implementation design[23] assesses the effectiveness of an intervention in a new clinical setting, while simultaneously collecting pilot implementation outcomes on feasibility, acceptability, and barriers/facilitators to implementation.[23] This study will use a mixed-methods, hybrid-effectiveness implementation design to evaluate the effectiveness and implementation of a paraprofessional-delivered intervention to address ART nonadherence and substance use in HIV care in SA.

Our preliminary conceptual framework is based on the RE-AIM model (Figure 1). This conceptual model is suggested to guide hybrid effectiveness-implementation trials and was selected due to its dual focus on effectiveness and implementation outcomes, its inclusion of patient-and provider-level outcomes, and its prior application to guide implementation in sub-Saharan Africa.[45,46] The RE-AIM model emphasizes an intervention's reach, effectiveness, adoption, implementation, and maintenance.

Figure 1. RE-AIM Framework.



B. Study Sample

Inclusion and exclusion criteria. The study plans to recruit and enroll approximately 60 individuals who meet the following inclusion criteria: (1) HIV positive and on ART; (2) 18 to 65 years of age; (3) Elevated substance use risk for any substance except tobacco (ASSIST score of ≥11 for alcohol or ≥4 for all other non-tobacco substances); and who meet one of the following four criteria: (1) did not attain viral suppression from first-line ART per local clinic standard in the past three months (VL>400 copies/mL); (2) on second-line treatment; (3) reinitiated on first-line treatment within the past three months; (4) had a pharmacy non-refill at least once in the past three months.

Exclusion criteria include: (1) severe risk/likely dependence for opiates (ASSIST: >26) because opiate substitution therapy may not be available; (2) severe alcohol dependence symptoms that may warrant medical management of potential withdrawal symptoms; (3) active untreated, major mental illness (with untreated psychosis or mania) that would interfere with the paraprofessional adapted intervention; (4) inability to provide informed consent, or complete procedures in English or isiXhosa; (5) currently enrolled in the Matrix program, or another substance use treatment program or research study, aimed at improving ART adherence or substance use; (6) in the third-trimester of pregnancy during screening or baseline.

Patients excluded due to an active untreated, major mental illness will be referred to appropriate services. Likewise, patients excluded due to substance use severity will be referred to higher level of care, such as local substance use treatment facilities. To follow real-world implementation, exclusion criteria for substance use severity was operationalized based on local substance use treatment guidelines for referral to a higher level of care.

Recruitment procedures. Participants will be recruited from HIV-positive patients who are currently receiving primary care at the Town II clinic. The study research assistant and field worker will coordinate subject recruitment through routine clinical screening, and potential participants will be screened for eligibility by a field worker or research assistant in conjunction with a parent study (010/204). Potentially eligible patients (identified by their HIV primary care

clinic as failing first line treatment in the past 3 months: VL > 400 copies/mL, on second-line treatment, reinitiated on first-line treatment within the past three months, or pharmacy non-refill at least once in the past three months) will be screened for substance use. Eligible patients will be briefed on study procedures, and if interested, will provide informed consent. All individuals meeting inclusion criteria will be provided the opportunity to participate.

Based upon preliminary studies and published work screening for substance use in HIV care[7,26,27] the study estimates to recruit 1-2 eligible patients per week. At this rate, the study can conservatively estimate recruiting and randomizing 60 patients feasibly within 1.5 years.

Retention. Bilingual research assistants will track retention. Staff will be trained to place reminder calls to participants 1 week and then three days prior to each scheduled follow-up session. This approach has been used successfully in past work by the US team, and has achieved an 84% retention rate at 3-month follow-up. Each participant will also be asked for updated contact information (e.g. phone number, address) at each follow-up assessment to ascertain if phone numbers have changed.

C. Study Procedures

Study setting. This study will be conducted through the University of Cape Town (UCT). The proposed clinic (where Phase 1 data collection also occurred) and where the parent study (010/2014) is being conducted is the Town II clinic in Khayelitsha.

Consent procedures. Potentially eligible patients identified by their HIV primary care clinic as either (a) having a VL > 400 copies/mL, (b) being on second-line treatment, (c) having been reinitiated on first-line treatment within the past three months, or (d) having a pharmacy non-refill at least once in the past three months, will be screened for substance use by the research assistant or field worker using the WHO-ASSIST. If preliminary criteria are met, eligible patients will be briefed on study procedures; if interested, they will provide informed consent. Before signing the consent form, participants will receive a comprehensive and interactive explanation of the study by staff. Study personnel will receive training regarding procedures required to obtain informed consent, and training and supervision will be completed on an ongoing basis to continually reinforce such procedures. All study personnel will also be appropriately trained in the ethical conduct of human subjects research and will be required to recertify annually.

The consent form will include all the study participations, information about potential risks and benefits of participation, and information regarding whom they can contact for further questions. It also will state that participation is voluntary, that participants can refuse to answer any question, that participants can withdraw from the study at any time, and that study participation is in no way related to their care received at the clinic. All participant questions will be answered before they are asked to sign the consent form. Additionally, patients who provide informed consent will also be invited to sign a release of information to allow access to their medical record for current ART regimen, time on ART, viral load, and CD4 count (for up to two years after study entry for study monitoring purposes). Participants will be provided with a copy of the consent form for their own records.

All procedures and protocols will be approved by the University of Cape Town HREC and the US-based site (University of Maryland) before study initiation. Study staff will review all informed consents within one week of their completion.

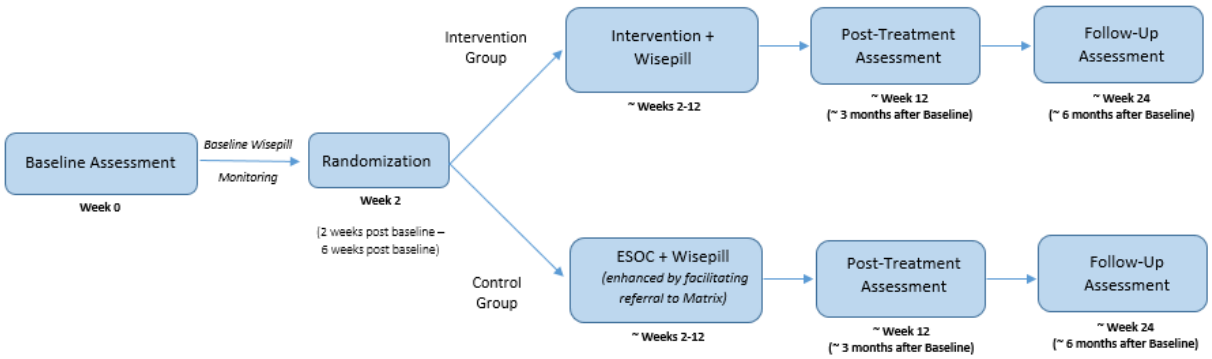
Study procedures. Study procedures are illustrated in Figure 2 (below). Participants who meet screening criteria and would like to be part of the study will go through an informed consent process, described above. Following consent procedures, participants will complete the baseline assessment. When the baseline assessment is finished, all eligible participants will receive a wireless adherence monitoring device, also known as Wisepill. Participants will then use the device for two weeks to enable two weeks of wireless medication monitoring as a baseline assessment of ART adherence. Approximately two weeks after the baseline

assessment, participants will be invited to come back to the clinic for randomization. Participants will be randomized into either 1) the intervention group (the paraprofessional adapted intervention to improve ART adherence and substance use) or 2) the control group (the enhanced standard of care). Randomization assignment will not affect patients' use of other ART clinic services. Regardless of condition, participants who attend all mandatory visits (intervention: all assessments and all six intervention sessions; control: all assessments and midpoint urinalysis) will receive a completion certificate at the end of their final assessment (six-month follow-up assessment).

Assessment visits. All participants will first attend a baseline assessment where they will begin monitoring their ART medications with Wisepill. Approximately two weeks later, participants will return to the clinic to undergo randomization. Those randomized into the intervention group will receive their first intervention visit, and have a total of six intervention sessions over a total of eight weeks. Those randomized into the control condition will receive an enhanced standard of care, described below. Approximately 3 months after the baseline assessment (and directly after intervention group members' last intervention visit), participants will come back to the clinic for a post-treatment assessment. They will return the Wisepill device at this assessment. Approximately 3 months after this assessment (6 months after baseline), participants will come in again for a final post-treatment assessment (6-month follow-up). Both post-treatment assessments will contain the same psychosocial self-report questionnaires as the baseline assessment (with exception of the demographic questionnaire) and the same biological assessments. Assessments and participant tracking will be done by bilingual research assistants. Participants will receive modest reimbursements for the follow-up assessments (150 Rand grocery voucher), and a 50 Rand reimbursement for local travel expenses to the study clinic will be provided for all non-major assessment visits.

When it is medically appropriate, the study will obtain permission from the participants to communicate their CD4 and viral load results and/or their struggles with substance use to their medical provider. This will only be done on a case-by-case basis, when, for example, study staff are aware that the clinic does not have the latest blood results of the participant or the participant needs more help with substance use than our study can offer. The study will only release this information with participants' permission, asking them to sign a medical release form. With this information, their provider can then make informed treatment decisions.

Figure 2: Study Design



Control Group (Enhanced Standard of Care). The control group will receive an enhanced standard of care (ESOC), which is a referral to a local substance use treatment clinic (there is a co-located Matrix[47,48] program at the recruitment site, which is an evidence-based 16-

week program to treat substance use). Although the Matrix model[47,48] was originally developed for stimulant use, there is accumulating research on its use for other substance types.[49,50] In the area where the study will occur, Matrix will be used as the preferred treatment for all substances so that the access to care for treatment-seeking patients is not restricted. While the majority of Matrix patients are primary meth ("tik") users (58%), some patients use other primary substances (alcohol, marijuana, heroin), and recent intake data has shown that over 60% of Matrix patients are using multiple substances.[35]

Patients' normal referral to Matrix will be enhanced for control participants by promoting follow up for the referral. Specifically, a referral note will be issued and study staff will either help the participant make an appointment as soon as possible or directly walk the participant across to Matrix, as the Matrix operates a walk-in screening approach. This follow up has been shown to boost referral attendance in this setting. The uptake of this referral will be assessed in the control condition through self-report at the follow-up assessments. Finally, those in the control group will also receive a Wisepill, the real-time electronic monitoring of ART device.

Intervention Group. The intervention group will receive the paraprofessional adapted intervention (a total of six sessions). Before the study begins, interventionists will undergo a week-long training in the intervention, which will be led by the U.S. investigator team in conjunction with the S. Africa investigators. For ease of use in the sessions, the intervention manual will be converted into a flip-chart in Xhosa. Each session will be approximately one hour long, and will contain problem solving for adherence, motivational interviewing, behavioural activation and mindfulness-based relapse prevention modules. The first four sessions will focus on new content, while the last two will review the first four sessions and focus on relapse prevention. The sessions are as follows:

- Session 1: *Life-Steps (Problem solving for Adherence).* Life-Steps[51,52] is a single-session counselling intervention for ART adherence. It is based on the general principles of cognitive-behavioral therapy and more specific principles of problem solving therapy.[51,52] Life-Steps has eleven components: (1) psychoeducation, (2) transportation to appointments, (3) obtaining medications, (4) communication with providers, (5) coping with side effects, (6) formulating a daily medication schedule, (7) medication storage, (8) cues for pill-taking, (9) imagery review of successful adherence in response to daily cues, (10) responses to slips in adherence, and (11) review of procedures. In this study, Life-Steps will be adapted to focus on myths/beliefs around mixing alcohol/drugs and ART. Specifically, this session will place a great emphasis on the beliefs participants have about how drug/alcohol use affects how ART works in their body, their understanding of what their doctors' messages have been around drugs/alcohol and ART, and how these beliefs relate to their desire to cut down on or stop alcohol/drug use.
- Session 2: *Increasing Motivation and Introduction to Behavioral Activation.* Session 2 will start out with a brief review of the previous session (Life-Steps), followed by a brief motivational exercise. More specifically, the participant will receive psychoeducation about substance use, and the interventionist and participant will discuss items including the extent to which substance use is causing problems in the participant's life and how substance use affects HIV disease progression. The interventionist and participant will also discuss the participant's goals for alcohol/drug use, how ready the participant is to change, and the pros and cons of change. Next, the interventionist will introduce the participant to behavioral activation for substance use, focusing on the cycle of negative reinforcement from substance use and how it disrupts HIV medication adherence. The interventionist will introduce behaviour monitoring in behavioural activation and end with a brief mindfulness exercise as an example of a healthy, substance free activity.
- Session 3: *Behavioral Activation Continued and Intro to Mindfulness Based Relapse Prevention (MBRP) Skills*: Session 3 will focus on behavioral activation and skills from mindfulness based relapse prevention (MBRP). The session will consist of checking in about

the participant's substance use and medication adherence, reviewing behavioral activation from the previous week, including continuing to identify health, substance-free rewarding activities in the patient's life. Next, basic skills of mindfulness-based relapse prevention will be introduced (i.e.., increase one's awareness of how craving feels in one's body, strategies for slowing down and not acting on urges/cravings, and coping with and responding to cravings in the moment). The session will end with a mindfulness exercise and participants are encouraged to schedule healthy, substance-free activities in between sessions.

- Session 4: *Mindfulness-based relapse prevention (MBRP).* The focus of Session 4 will be MBRP. In this session, the interventionist and participant will check in about the participant's substance use and medication adherence in the past week, review content from past sessions, and continue to build upon prior week's introduction to mindfulness-based relapse prevention strategies. This session will also end with a mindfulness exercise, which participants are encouraged to practice between sessions.
- Sessions 5 & 6: *Relapse prevention continued*. Sessions 5 and 6 will focus on reviewing the material learned in previous sessions and working more on relapse prevention. The interventionist and participant will check in about the participant's substance use and medication adherence in the previous week, review items learned in previous sessions, and plan ahead to prevent future relapse. Both sessions will end with a mindfulness exercise.
- *Optional Booster Sessions*: After completing the 6 intervention sessions, participants will be allowed to attend up to 6 booster sessions. These sessions must be completed after the 6th intervention session and before the six-month follow-up assessment. Booster sessions will consist of topics and skills from the previous 6 sessions to address any difficulties with adherence and/or substance use. The purpose of the booster sessions is to help those who may need additional time to reinforce the strategies of the intervention.

While it is preferred for intervention sessions to be done in person at the clinic, intervention participants who are unable to go to the clinic will have the option of telephone sessions. Allowing interventions over the phone will make the intervention accessible to participants who have difficulty traveling to the clinic or who may be traveling.

If a participant still has severe substance use symptoms at the end of the study period, the participant will receive a referral for a local Matrix clinic. Additionally, if a participant's symptoms worsen at any point of the study and a higher level of care is needed, the participant will also receive a referral for a local Matrix clinic.

Wisepill battery monitoring. Participants in both conditions will be contacted approximately half-way between their baseline assessment and the post-treatment assessment to check in on their use of the Wisepill device. The point of this check-in is to ensure that participants continue to use their Wisepill devices, to remind participants to bring their Wisepill devices back at the post-treatment assessment, and to ensure that participants continue to charge their Wisepill devices. Although participants will only use the device for approximately 3 months and the battery life of a Wisepill device lasts approximately 4 months, participants will still be asked to charge their Wisepill device to ensure that no valuable data is lost. These check-ins may happen over the telephone or, in the event that the participant is at the clinic, on site.

D. Primary, secondary, and other outcome measures.

Primary, secondary, and other outcomes are specified below (separate primary outcomes to evaluate implementation and effectiveness). Non-primary assessment measures will be used as potential covariates for primary analyses and/or mechanisms of intervention effectiveness.

1. Primary & Secondary Outcomes

A. HIV Medication Adherence

a. Title: Electronic monitoring (Wisepill)
Description: Wisepill is a real-time, wireless, electronic adherence monitoring device used to assess ART adherence in real time.[54,55] Wisepill uses cell phone technology to transmit a real-time signal to a web server when the pill box is opened. Participants do not need to come into the clinic for the study to obtain readings. A dose will be considered 'taken' if the box is opened ± 2 hours from the prescribed time.[54] The study will also use the recommended methods for Wisepill data collection and analysis, which are to adjust for technical malfunctions, loss of signal, and self-reported pocket doses.[54,55] Participants in both conditions will be given a Wisepill box at the baseline visit, and the 2-week period between baseline and randomization will serve as the baseline adherence measure. We will calculate % doses missed vs. prescribed. Participants will use the Wisepill box during the first three months of the study (which maps onto the intervention period), and return the device at their post-treatment assessment.
Time Frame: Approximately 10-weeks post-randomization (post-intervention assessment)

B. Substance Use

a. Title: Biological measure of substance use (alcohol, drugs)
Description: Biological measure of substance use. Drug use will be assessed using urinalysis (rapid detect 6-panel urine tests (cocaine, marijuana, amphetamines, opiates, phencyclidine, alcohol).
Time Frame: Approximately 10-weeks post-randomization (post-treatment assessment, primary outcome) and 22-weeks post-randomization (6-month follow-up assessment, secondary outcome)

b. Title: WHO-ASSIST
Description: Score on the Alcohol, Smoking, and Substance Involvement Screening Test (WHO-ASSIST). The WHO-ASSIST was developed for the World Health Organization (WHO), and is used to detect and manage substance use and related problems in primary and general medical care settings. The test screens for alcohol, cannabis, cocaine, opiates, amphetamines, hallucinogens, and other drug-related problems in primary care and has been validated in South Africa. It categorizes individuals into low (0-3 for illicit drug use), moderate (4-26 for illicit drug use), or high risk (>26 for illicit drug use) for substance use related problems.
Time Frame: Approximately 10-weeks post-randomization (post-treatment assessment: primary outcome) and 22-weeks post-randomization (6-month follow-up assessment: secondary outcome)

C. Feasibility & Acceptability of Intervention

a. Title: Provider fidelity
Description: Provider fidelity to intervention delivery, assessed by an independent assessor. This will be assessed on an ongoing basis throughout the intervention period (Sessions 1-6). Intervention sessions will be audiotaped, and a minimum of 20% of tapes will be translated and reviewed an independent rater. Fidelity ratings will be based on previously validated assessment[53] of therapist adherence and competency, which will be adapted

for the specific intervention components and context, as has been done previously in sub-Saharan Africa.[33] Following recommendations for implementation science research,[6] a "fidelity score" will be calculated based on the proportion of key intervention components delivered as intended across sessions.
Time Frame: Measured ongoing from first intervention participant's intervention session until last intervention session for final participant

b. Title: Participant participation and retention
Description: The percentage of participants assigned to the intervention who agree to enroll in the intervention, the percentage of these attending ≥75% of sessions, and the percentage who dropped out of treatment. This method of assessing participation and retention follows recommendations from a prior effectiveness-implementation trial,[51] and the rates of our patient participation and retention will be compared with other similar pilot trials.[33,57]
Time Frame: Measured ongoing from first intervention participant's randomization until about 10-weeks post-randomization for the final intervention participant. Final overall measurement at about 10-weeks post-randomization for the final intervention participant.

2. Other Outcome Measures

These measures were based upon the qualitative findings from Phase 1 and existing literature. The following measures include potential covariates, potential mechanisms of intervention effectiveness, and exploratory outcomes. Please see Table 1 below for when each assessment measure is administered and Table 2 below for when each weekly measure is administered.

1. Demographics: At baseline, participants will answer a questionnaire about basic demographics, including questions regarding age, sex, race, sexual orientation, and educational history.
2. Mode of HIV Infection: At baseline, participants will be asked a single-item (six subpart) ACTG question assessing risk factors for likelihood of means of HIV infection.
3. Economics & Resource Utilization: At all major assessments, participants will answer a questionnaire about economics and resource utilization. They will be asked about items that include their approximate monthly household income, their current work situation, their household's spending habits, if they own objects such as cell phones, how they get to the clinic, how much money it costs them to go to the clinic, and if they use any other clinics or other health services outside of the clinic. This will be used to inform future cost effectiveness analyses of the intervention.
4. AUDIT. The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening tool also developed by the World Health Organization (WHO), and is used to specifically assess alcohol consumption, drinking behaviors, and alcohol-related problems.
5. Ira Wilson's Three-Item Self-Report Measure: Ira Wilson's Three-Item Self-Report Measure is a 3-item self-report scale used to assess antiretroviral therapy adherence.[56] The scale has a Cronbach's alpha of 0.83 for HIV medication. This measure will be given at all major assessments.
6. Interactive Toxicity Beliefs: At all major assessments, participants will answer 4 questions about their beliefs regarding combining substances and antiretroviral

therapy. These questions were included following our findings from Phase 1 and are based on prior research on interactive toxicity beliefs in Uganda.[59]

7. Behavioral Activation for Depression Scale (BADS): This 25-item measure tracks weekly changes in the behaviors hypothesized to explain the effectiveness of a behavioral activation intervention. It examines activation, avoidance/rumination, work/school impairment, and social impairment.[60] BADS will be given at all major assessments to measure a potential mechanism of intervention effectiveness.
8. Barriers to Adherence: Participants will answer questions about barriers to their antiretroviral therapy adherence at all major visits. Reasons for non-adherence include wanting to avoid side effects, not having food with which to take the medication, sharing the medication with others, forgetting, forgetting due to alcohol use or drug use, fear of stigmatization, and an open-ended "other." This measure will be given at all major assessments.
9. Robbed, Recreational ARVs: At baseline, participants will be asked if anyone has ever tried to steal their ARVs from them, or if they have ever used their ARVs recreationally. At the follow-up assessments, participants will be asked the same two questions regarding the past 3 months.
10. Brief RCope: This 14-item measure assesses how participants use religion to cope with stressors[61] that has been shown to strongly correlate with substance use in this population. Participants will fill out this scale at all major assessments.
11. Penn Craving Scale: This five-item, self-report measure asks participants about the frequency, intensity and duration of their craving (for alcohol and/or other drugs), and how well they are able to resist drinking and/or using.[62] For alcohol vs. other drug use, the items in both craving scales are identical, with the exception of using the word "alcohol" or "drugs." This scale will be administered at all major assessments.
12. Patient Health Questionnaire (PHQ-9): This 9-item measure of depression[63] has been shown to be a good outcome measure of depression.[64] It will be used at all major assessments to assess participants' depression, which is highly comorbid with HIV and substance use disorders.
13. Reinforcement-Punishment Inventory (RPI): This 20-item measure assesses reinforcement in one's environment and is a potential mechanism of behavioral activation interventions.[65] It will be used at all major assessments as a potential mechanism of intervention effectiveness.
14. Perseverative Thinking Questionnaire (PTQ): This 15-item measure assesses "thinking too much" (i.e., rumination and/or worry), which is a primary target of mindfulness-based interventions. It will be used at all major assessments.[66]
15. Sexual Risk Taking: Participants will answer questions about their sexual risk taking behaviors at all major assessments. Items include questions about number of sexual partners, sexual partners' HIV status, and condom use. This is being used to identify the level of HIV transmission risk among individuals who have detectable HIV virus.
16. Shortened Inventory of Problems – Alcohol, Drugs (SIP-AD): This 15-item measure examines perceived adverse consequences of substance use.[67] It will be used at all major assessments to identify the impact of the intervention on problems associated with substance use.
17. Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) –: This scale assesses participant motivation to change alcohol use or other drug use behavior.[68] It will be used at all major assessments (alcohol use and drug use are asked separately) and is an important covariate and potential moderator of intervention effectiveness.

18. Substance Use History and Substance Use Treatment Utilization: Substance use history at baseline will ask participants about their lifetime substance use history, while the measure at both follow-up visits will ask participants about their substance use treatment utilization since their last assessment visit. Items include questions about referrals to treatment, money spent in the last 30 days on substances, incarcerations related to substances, and how much participants would pay for a day free of problems from alcohol/drugs.
19. Substance Use and HIV Stigma (SU-SMS and SU-SMS HIV): These self-report measures assess beliefs about personal alcohol use and HIV related stigma (administered separately), which was identified in Phase 1 as a major barrier to integration of HIV and substance use treatment services.[69,70] This measure will be given at all major assessments.
20. AIDS Clinical Trials Group 21-Item Short Form Survey (ACTG SF-21): This 21-item survey assesses general quality of life in people living with HIV.[71] This scale is broken up into several subscales: physical functioning, role functioning, pain, current health perceptions, emotional well-being, cognitive functioning, energy/fatigue, and social functioning.[64] This survey will be used at all major assessments to also be included to inform future cost effectiveness analyses.
21. Acceptability & Feasibility Questionnaire: At the post-treatment assessment, intervention participants will answer questions about how acceptable and feasible they found the intervention. This measure is derived from a validated measure of acceptability and feasibility developed by the Applied Mental Health Research Group at Johns Hopkins.[58] At the 6-month follow-up, participants will be asked only about continuation of skill use from the intervention.
22. Semi-structured intervention exit interviews: To supplement and allow for interpretation of the quantitative implementation outcomes, a six-month follow up qualitative assessment will also be conducted following some of the intervention participants randomized to the intervention condition (up to *n*= 30) to assess perceptions of acceptability and feasibility of the intervention.
23. Semi-structured provider interviews: To better understand the feasibility and acceptability of the intervention and barriers to implementation, individual interviews will be conducted with up to 11 providers at Town II Clinic. These interviews may be conducted in-person or over the phone.
24. Semi-structured control exit interviews: To supplement and allow for a better understanding of quantitative outcomes, individual interviews will also be conducted with control participants after the six-month follow up assessment. A maximum of 30 interviews will be conducted.
25. Timeline Followback. The Timeline Followback[72] method is a technique for assessing substance use. The method consists of an interview where participants reference a calendar to estimate their daily substance use over a specified period of time. The method has been successful in assessing both alcohol[72] and drug[73] use. In the present study, the calendar used will be derived from the participants' Wisepill output (i.e., indicating the days doses were missed) to further aid participants in remembering their substance use, and to help participants and researchers understand how substance use impacts antiretroviral therapy adherence. Timeline Followback will be used at all major assessment visits and at each intervention session
26. SRA Weekly Adherence: At each intervention session, participants will answer 2 self-report questions to assess their HIV medication adherence in the past week.

3. Other Collected Data:

1. CD4 count and Viral Load: CD4 count and viral load will be extracted from participants' medical record at each major visit. If results are not available within 3 months of the baseline assessment and 30 days of the follow-up assessments (post-treatment assessment and 6-month follow-up assessment), participants will be invited to undergo a blood draw. These procedures will not add any cost to the patient. CD4 count will be used as a measure of immune function and disease progression. Viral load will be used as a biological indicator of ART adherence. Viral load will also be used to document the percentage of the sample with virological suppression (measured dichotomously at < 400 copies/mL).
2. Dried Blood Spot (DBS): We will be collecting and storing dried blood spots. Analysis by DBS will allow for a gross confirmation that at least some recent ART is present in the system.[79] This biological confirmation will be used as verification of Wisepill data. One vial of blood for DBS will be taken at each major assessment. In addition to adherence, we are storing DBS for future biomarkers in our freezer. We will ship and then destroy samples before five years after the study is completed.
3. Urinalysis. Urinalysis will be used as a biological indicator of alcohol and drug use. Urinalysis will be conducted at all major assessments (baseline, post-treatment assessment, 6-months follow-up assessment) and at intervention participants' third session (halfway through the intervention) by a trained research assistant using rapid detect urine tests. Control participants will also be asked to come into the clinic for urinalysis between their baseline and post-treatment assessment (approximately 5-weeks post-randomization). These urine tests detect cocaine, marijuana, amphetamines, opiates, phencyclidine and alcohol, and give dichotomous results. Since there is potential sigma related to substance use, and participants may falsely believe that ART will be withheld in the context of use,[66] study procedures include dialogue with the participant to ensuring anonymity of the results.
4. Chart Extraction: Patients who provide informed consent will also be invited to sign a release of information to allow access to their medical record for current ART regimen, time on ART, viral load, CD4 count, tuberculosis (TB) treatment information, mental health information (including diagnoses and substance use treatment referrals) and appointment attendance (HIV treatment program and Matrix if applicable). This information will be specifically extracted from their medical charts at all major assessments.

E. Data analytic plan.

Power calculation and sample size.

The study plans to enroll 60 participants. The main analysis which the sample size calculation was based on is the effect of the intervention vs. enhanced standard of care on ART nonadherence (Wisepill) at 6 months. Previous objective measures of ART adherence in substance using populations have estimated average adherence of approximately 55% with a standard deviation of 0.25.[74-76] Assuming similar characteristics in standard of care, and based on a sample size of 30 in each arm as recommended as the upper limit sample size for pilot RCTs, the study will have 80% power to detect an 18% difference in objectively measured ART adherence between study arms using a two-sided test with an alpha level of 0.05. Given that the intervention will be adapted and has not been implemented prior in this setting, the table has been included below to demonstrate the levels of power based on varying differences in average adherence that may be detected between groups. These estimates are based on 30

participants in each arm, in keeping with the recommendations for pilot RCTs and pilot,[77] Type I hybrid-effectiveness-implementation designs.[23,53]

Data analytic plan.

Quantitative longitudinal analysis will examine changes in primary effectiveness outcomes: 1) ART nonadherence; 2) substance use; 3) and viral load (exploratory) from baseline to 6-month follow-up between the conditions. Descriptive measures will be used to summarize data (e.g., means, SD, median, IQR for continuous variables). Exact binomial confidence intervals will be used to estimate confidence intervals for categorical variables. Statistical tests (such as t-test and Wilcoxon rank sum test) will be used to compare continuous study outcomes (e.g., ART nonadherence) between the two arms at baseline. For comparison of categorical outcomes (e.g., urinalysis), Fisher's exact test will be used. Longitudinal data analysis using generalized linear mixed models (GLMM) will be used to compare the study endpoints (ART nonadherence, substance use, viral load at 6 months) between the two arms after adjusting for the effect of other covariates (e.g., gender, age). This approach increases power by including all available data points. Intent-to-treat will be utilized, where all individuals will be analyzed according to the condition that they were randomized. Effect size estimates will be generated to provide estimates to power for a larger future grant application.

Table 1. Levels of power based on varying differences in adherence detected.

Predicted Avg Adherence in Control Group	Predicted Avg Adherence in Tx Group	Difference in Avg Adherence	SD of Estimated Adherence	Power
0.55	0.85	0.30	0.25	0.99
0.55	0.80	0.25	0.25	0.97
0.55	0.75	0.20	0.25	0.88
0.55	0.73	0.18	0.25	0.80
0.55	0.70	0.15	0.25	0.64
0.55	0.65	0.10	0.25	0.34

ETHICAL CONSIDERATIONS AND RISKS TO THE SUBJECTS

A. Risks to participants.

Human subjects involvement and characteristics.

Participants will be HIV-positive men and women, between 18 and 65 years of age, who have an elevated substance use risk, excluding tobacco, as determined by a WHO-ASSIST score of ≥4 (for all non-tobacco substances) or an ASSIST score of ≥11 for alcohol, and who either (a) did not attain viral suppression from first-line ART per local clinic standard (VL>400 copies/mL), (b) are on second-line treatment, (c) were reinitiated on first-line treatment within the past three months, or (d) had a pharmacy non-refill at least once in the past three months. All participants also must *not* be at a severe risk for dependence for opiates, as determined by a WHO-ASSIST score of >26, may not have severe alcohol dependence symptoms, and must be able to provide informed consent. Based upon results of Phase 1 and other preliminary data at the recruitment site, it is anticipated that participants will be 95% Black African, and 5% will be the South African demographic group of “coloured” (the NIH category of more than one race). Also based upon results of Phase 1 and other preliminary data at the recruitment site, it is anticipated that 50% of the sample will be women.

The field worker and research assistant will coordinate the subject recruitment. Interested potential participants recruited through the clinic will speak with the research assistant or field worker to do a brief initial screen. If preliminary criteria are met and the participant is still interested in joining the study, the participant will complete the informed consent process and a baseline assessment (explained above).

If the participant is eligible for the study and provides consent to participate in the study, the participant will be given a Wisepill container and Wisepill instructions after the baseline assessment, conducted by the study research assistant. Participants will then be scheduled for a randomization visit, approximately two weeks after the baseline assessment. At the randomization visit, participants will be randomized into either the control group (enhanced standard of care group) or the intervention group, as described above.

Participants randomized to the intervention condition will have six individual counseling sessions over the course of 6-8 weeks. These sessions will focus on using improving ART adherence and substance use. All participants will have two post-treatment assessments, one immediately after the intervention (the post-treatment assessment, about three months after baseline), and a second six months after baseline (six-month follow-up assessment). At each of these assessments, participants will repeat the assessment they took at baseline, with the exception of the demographics section and the addition of self-report section about the acceptability of the program (the intervention for the intervention group, or the utilization of the Matrix program for the control participants who were referred to Matrix).

Sources of material.

Data will be obtained from patients recruited specifically for this protocol, including self-report assessment and biological assessments. A trained research assistant will conduct follow-up assessments. Chart information will also be extracted from medical records to determine HIV outcomes and other relevant information (e.g., tuberculosis information, mental health diagnoses, previous substance use treatment referrals), and whether individuals followed up on our substance use treatment referral.

Therapy training and supervision.

The therapy manual was systematically developed and adapted based on preliminary studies and formative work in Phase 1. Specifically, the therapist manual was adapted into a flip-chart format for ease of use for the interventionists. Dr. Magidson will be the primary trainer and supervisor of the interventionists in consultation with Drs. Andersen, Safren, Myers, and Joska and supervision and training will co-led by Dr. Magidson's UMD research team. Supervision will be a multi-day training with proficiency testing and booster trainings scheduled as needed based on ongoing proficiency testing and review. Ongoing supervision will be achieved through regular Skype meetings, audiotape review, and site visits to provide in-person training and supervision as needed.

Foreseeable risks and discomforts

It is unlikely that participants will be at any risk for physical harm as a result of study participation. Participants may find some of the questions asked in the interview or assessment to be emotionally upsetting and may experience short-term elevations in negative affect during active treatment sessions. As with any study of participants with substance use, there is always the risk of symptoms worsening. At any point in the study if a patient exhibits increasing substance use severity that warrants a higher level of care, they will be referred to a local substance use treatment facility. Given that this is standard of care at the recruitment site (Town II), a referral system is already in place. If withdrawal symptoms require immediate medical management, patients will be brought to the nearest emergency room.

Participants with HIV viral load or CD4 cell counts missing from their medical record within 3 months prior to their baseline assessment or within 30 days prior to their follow-up assessments (post-treatment assessment and 6-month follow-up assessment) will be invited to undergo a blood draw at all major visits to provide 3 vials of blood. The blood draw procedures will be carried out by staff trained in phlebotomy to minimize the accidental injury or discomfort to the

participants. Potential risks to subjects could include bleeding, swelling or bruising at the site of the blood draw.

Other potential risks include possibility that confidentiality could be breached, discomfort about the treatment sessions and assessments being audio-recorded for supervision and treatment adherence review purposes, and the possibility of treatment non-response or relapse/recurrence. A discussion of how risks will further be minimized is described below.

B. Minimization of risks.

It is unlikely that participants will be at any risk for physical harm as a result of study participation. The design of the current study provides an evidence-based intervention for ART adherence and substance use in the experimental condition, a referral option for substance use treatment and efforts to promote follow up on this referral in both conditions, and monitoring of symptoms in both conditions. The interventions will be implemented by bilingual interventionists who will be trained in the study protocol. Treatment fidelity procedures will help ensure that clinical protocols are being implemented as designed. Study interventionists will receive specific training to address distress related to substance use and HIV management. They will also receive focused training on screening for substance use and in particular the detection of severe symptoms that may warrant medical management.

Informed Consent

All participants will complete informed consent procedures, as described above. To join the study, participants must fully understand and sign the consent form. The participant will have as much time as they want to review the consent form and ask questions. A study staff member will also review the form with each participant. The consent form will include all study procedures, information about potential risks and benefits of participation, and information regarding whom they can contact for further questions. It will also state that participation is voluntary, that participants can refuse to answer any question, that participants can withdraw from the study at any time, and that study participation is in no way related to the care they receive at the clinic. All procedures and protocols will be approved by the coordinating site University of Maryland IRB and the University of Cape Town HREC before study initiation.

Distress

Additional procedures will be in place to further protect participants who may experience higher than usual levels of distress, regardless of treatment assignment. Interventionists and assessors will be trained by Dr. Magidson in consultation with Drs. Andersen, Joska and Myers to be vigilant and sensitive to signs of distress in our participants, as well as signs of substance use withdrawal symptoms.

Worsening symptoms.

For those in the integrated treatment condition, interventionists will be free to deviate from the protocol to ensure participant safety. Referrals will be made for a higher level of care if at any point symptoms worsen and are no longer manageable with the integrated treatment alone, or if withdrawal symptoms require medical attention. For those in the control condition, if there are increases in severity of substance use and/or signs of potentially medically dangerous withdrawal symptoms at study visits, the independent assessor will make appropriate referrals for next-level of care. In addition, Drs. Bronwyn Myers and Lena Andersen are clinical psychologists with specializations in addiction and mental health concerns, respectively. They will be contactable by cell phone in the case of emergency to provide supervision if required. Further, there are community health psychologists and psychiatrists in the clinic where recruitment will occur who will be available in the case of emergency. In the event that a higher level of substance use treatment is required, there are substance use treatment clinics that

regularly receive referrals from the clinic site where recruitment will occur (i.e., Matrix), and there are existing protocols in place for making this referral. If an inpatient level of care or emergency services is required for management of withdrawal symptoms, treatment is available at either of two local area hospitals in Cape Town, a short distant from both clinic sites: G.F. Jooste Hospital and Karl Bremer Hospital. In the event that study participants need this level of care, transport will be arranged for them in-line with clinic protocols either through the Health Transport System NetCare or by ambulance. Referral options may also include referral to mental health and social sector services. Study procedures do not preclude participant referral for additional care and treatment and in each case where additional levels of care are required, decisions regarding the participant's continuation in the study will be based solely on a consideration of the participants' welfare. In both conditions, referrals for substance use treatment and/or a higher level care will also be made at the end of the study period if severe symptoms are present.

Finally, the exclusion criterion for participants with severe dependence symptoms that may warrant medical attention and/or opiate dependence ensures that those who would be most likely to experience serious physiological withdrawal symptoms are not enrolled. Any patient excluded from study procedures due to severity of substance use will also be offered a referral to a local substance use clinic or to a higher level of care.

Blood draws.

Participants will be invited to give a blood sample for dried blood spots (1 vial) and when CD4 count and viral load results are not available in the past 3 months at the baseline assessment or in the past 30 days at the follow-up assessments (1 vial each for CD4 and viral load). The blood draw procedures will be carried out by trained phlebotomists, nurses or physicians at the ART clinic settings to minimize the accidental injury or discomfort to the participants. Participants who experience harm as a result of these procedures will receive first aid from study staff and referral to medical professional if needed.

Confidentiality.

In terms of confidentiality, all data will be kept confidential, under lock-and-key (or password protected only to authorized staff) which will change periodically, accessible only to specified study staff. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept separately under lock and key or password protection. As part of the informed consent process and throughout the study therapy and assessment procedures, all participants will be advised that they may decline to answer any study questions. These procedures will be implemented to provide study participants with the assurance of confidentiality around very sensitive and personal information relating to their mental health and substance use, sexual and substance use history, and HIV status. All study personnel working on the project will be educated about the importance of strictly respecting participants' rights to confidentiality and will have completed study specific trainings.

Additionally, urinalysis will be conducted by a trained research assistant in a private area of the clinic using six-panel urinalysis alcohol and drug testing kits. All testing results will be confidential, available only to the study staff, and will not be documented in the patient's medical record. It is indicated in the consent form that the drug results will only be available to the research study staff and will not be shared with the clinic providers nor the study interventionist unless requested by the patient.

Audio files may be transcribed to written text using a secure transcription service. All audio files sent for transcription will be de-identified and saved only using participant ID numbers in order to protect participants' confidentiality. Team members at the University of Maryland will only use the transcription services for assistance; they will still check and correct any errors in the transcripts from the service. Either Otter.ai (by AISense) or Home Row Inc. will be used for

transcription services. Otter.ai uses artificial intelligence technology and syncs data over an encrypted connection and stores it in a secure data center that has both physical and electronic security. When the user deletes the recording, there will be no record retained by AISense. Home Row Inc. offers military-grade 128-bit Secure Socket Layer (SSL) encryption security in transit and 256-bit AES at rest. Their typists are carefully vetted industry United States veterans who work under strict non-disclosure agreements, and all audio files are promptly and permanently deleted from servers as each project is completed.

Summary.

To emphasize, in the case of treatment non-response or other deterioration or relapse, the interventionists or assessors will refer patients to appropriate clinical care. Participants who begin treatment and experience adverse outcomes sufficient to require removal from the study will also receive linkage to an appropriate level of clinical care. The exact nature of "appropriate clinical care" will be determined by the judgment of clinicians familiar with the specific participant and may include substance use treatment referrals, arrangements for evaluation in a local Emergency Department, or referrals to partial hospital or inpatient levels of care.

C. Expected benefits.

Although it is possible that there will be no direct benefit to participants in the study, they may benefit from the close monitoring of substance use and ART adherence. Participants assigned to the integrated treatment condition may benefit from the interventions provided to address substance use and support improvements in their ART medication adherence. Information provided as part of the treatment program may also help participants better understand ART adherence, their substance use, and maintain improvement over the long-term.

All participants will have the opportunity to participate in active treatment for ART medication adherence and receive a referral for substance use treatment outside of the study. Participants are also provided with a small amount of financial remuneration for completing their participation. It is hypothesized that the active treatment will be associated, on average, with beneficial effects for both substance use and medication adherence and it is anticipated that some of our study participants may reap these benefits.

D. Participant remuneration.

Participants will be given a 150 Rand (~$5 USD) grocery voucher for each assessment. At the post-treatment assessment, participants must return their Wisepill Devices to receive the grocery voucher. If a participant forgets his/her Wisepill at this visit, he/she will be given the voucher whenever he/she returns the device. Travel costs will also be reimbursed for all non-major visits (50 Rand).

E. Data monitoring & management procedures.

Data acquisition and transmission.

Assessment integrity.

All assessments will be conducted by a trained study research assistant who will be trained and supervised throughout the study by the project director.

Treatment sessions.

Recording of treatment sessions will be a required procedure to ensure appropriate monitoring and supervision for interventionists. The purpose of the recording will be explained, confidentiality will be respected, and both informed consent and authorization for recording will be obtained. All digital audio recordings of therapy sessions will be uploaded to the study computer immediately following the session and the audio file deleted from the digital recorder. Computer audio files will be secured by password and will be accessed only by authorized study

personnel (i.e., PI, site-PI, the study staff member conducting the fidelity check). Digital recordings will be stored and moved between sites using a secure, password-protected and HIPAA-compliant website. For fidelity purposes, approximately 20% of recordings will be translated into English by a bilingual research assistant, and all personal information relating to the participant will be removed. Recordings will be maintained until five years after the publication of study results in line with the guidelines of the American Psychological Association.

Data acquisition and transmission.

Data collection occurs only in South Africa at the specified data collection site. Data will be obtained from patients recruited specifically for this protocol, including self- report assessments administered via computer, medical chart review, and biological assessments when relevant clinical data is not available in chart review. All data will be directly entered into an electronic REDCap database. All participants will be given a study ID. Identifying and personal information of study participants will be kept entirely separate from their coded data. Lastly, the database administrator will export requested data to the investigators in a de-identified file format that can be easily read by most statistical packages. In addition, data on interventionist training, independent assessor training, clinical supervision, participant progress through the study procedures will also be entered and uploaded into REDCap.

Data entry methods.

Data collection occurs only at the Cape Town study implementation site. Data entry will occur as close to real time as possible to facilitate data management and monitoring of study operations. The Research Assistant at the University of Maryland site will provide regular reports to Dr. Magidson.

REDCap

All data entry will utilize REDCap, a software toolset and workflow methodology for electronic collection and management of research and clinical trial data in real-time. REDCap provides a web-based application with an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. REDCap data collection projects data on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the University of Maryland. All information entered on REDCap will be de-identified in order to protect participants' identities.

Quality assurance

Data completeness.

To ensure the usability of self-report data, the research assistant will review all self-report measures to ensure their completeness. Using an electronic data capture system such as REDCap is meant to reduce errors in the data entry and management process. Using REDCap, missing data can be reduced by making items required to answer before moving on to the next item and effort and error associated with data entry can be reduced because there is no manual entering of data by research assistants. A secure database that is password-protected will be kept and located on a secure server on a local network at UCT. Confidentiality can be ensured as identifying and personal information of study participants will be kept entirely separate from their coded data. Lastly, the database administrator will export requested data to the investigators in a file format that can be easily read by most statistical packages.

Treatment sessions.

A subset of treatment sessions will be audio-taped and 20% (of all intervention sessions)

will be rated shortly thereafter by independent raters to assess therapist adherence to, and competence with, the protocol, using rating checklists and scales developed for this use. Weekly clinical supervision will be provided by Dr. Magidson and her team at UMD. Supervision will include reviewing translated session recordings. Audio recordings of selected translated sessions will be made available for download using secure file transfer.

Regular reports.

Regular reports will be generated and monitored by the PI to ensure validity and integrity of the data at all phases of the study, including:

Activity	Report Generated	Monitoring by PI
Study recruitment and retention	Research Meeting Report - RA to study team	Monitored frequently by PI at research team meetings
Enrollment and Randomization	Research meeting report of enrollment updates (inclusion and exclusion criteria) and tracking of assignment to condition	Monitored frequently by PI at research team meetings
Self-report data	RA will review data at participants' visits for completeness, accurate downloading of data, and tracking	Monitored frequently by PI at research team meetings
Intervention	A random selection of 20% of sessions for each therapist will be reviewed for therapist adherence to protocol by PI	Monitored at frequent clinical supervision

Confidentiality.

Confidentiality is assured as participants will be identified on all study materials only by participant number, visit number, and date of visit. By recording the study data in this manner, the information can be considered 'de-identified.'

F. Data safety and monitoring plan.

Regulatory Issues

The following procedures will be followed, in compliance with NIH requirements, to ensure the safety of study participants and the validity and integrity of data.

Mechanisms for reporting adverse events.

Adverse events are defined as harmful occurrences to study participants, either study related or non-study related.

At yearly intervals during the course of the study and then again at its completion, unblinded summaries of the numbers and rates of adverse events by treatment group will be summarized by the research team. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed.

Reporting of SAEs to the IRB and NIDA.

Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs; i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any

congenital anomaly). This also includes any event that a study investigator or the DSM Committee judges to impose a significant hazard, contraindication, side effect, or precaution. Additional reporting to site-specific IRBs will be done within 24 hours of the study team being made aware of the SAE. Reporting of any study-related SAEs and SAEs that severely impact participants (i.e., participant deaths) will be made to NIDA within 24-72 hours of the study team being made aware of the SAE.

Reporting of IRB actions to NIDA.

The principal investigator will report, via email, and, if appropriate hard copies of action logs or reports, of any major IRB actions. These will also be reported on the written, yearly progress report to NIDA. Minor amendments (i.e. advertisements, minor changes to procedures) are not regularly reported to NIDA.

Report of changes or amendments to the protocol.

Any changes to the protocol or amendments will be submitted to the IRB before they are implemented. For each yearly annual review, the detailed protocol will be updated and sent to the IRB as well.

Following guidelines by NIH, the NIDA project officer will be kept informed of any major changes to the protocol prior to being conducted via email from the principal investigator to the project officer. This will include any changes involving key personnel. Additionally, these changes will be recorded in the annual progress report submitted to the NIDA project officer.

Trial stopping rules.

There are no articulated stopping rules in advance of this study (i.e. for futility or for a stronger than expected effect). However, if at any time during the course of the study the Committee judges that risk to subjects outweighs the potential benefits, the Committee shall have the discretion and responsibility to recommend that the study be terminated. In such cases, the PI will immediately consult the DSM committee and consider the most appropriate course of action up to and including the immediate discontinuation of the intervention. There is no pre-specified stopping rule given the low anticipated risk of participation and small sample size. The power analysis is such that the full N would be required to make this determination. However, as with any DSMB, this DSMB will have the power to request analyses, post-randomization data, or any other information about the study, and has the power to suspend the study should they deem it necessary and a potential participant safety issue.

Disclosure of any conflict of interest.

Each investigator has completed a conflict of interest statement, which is kept on file by the study team and has been submitted to their respective institutions' IRBs. Any new investigators or key study staff will complete these forms, which will be stored kept on record. Any changes to conflict of interest statements will be reported to NIDA. Conflicts of interest will be disclosed to the DSMB at the time of each report. There are no financial conflicts of interests in this behavioral study, and no other conflicts of interests at this time.

Collection and reporting of AEs to SAEs

All staff will receive extensive training on ascertaining, monitoring, and documenting adverse events. The K23 mentors have extensive experience in clinical trials organization and management, including data safety monitoring for single site and multi-site trials. All investigators and study staff will be trained in monitoring and documenting adverse events. Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs). This also includes any event that a study investigator judges to impose a significant hazard or precaution. The study sites will report AEs and SAEs to the UCT site PI, Dr. Joska,

and PI Dr. Magidson.

AEs will be labelled according to severity, which is based on their impact on the patient. An AE will be termed “mild” if it does not have a major impact on the patient, “moderate” if it causes the patient some minor inconvenience, and “severe” if it causes a substantial disruption to the patient’s well-being. A severe AE and an SAE are distinct terms. A subject could experience a severe AE that does not meet the above-listed definition of an SAE; alternatively, a subject could experience a moderate AE that meets the SAE definition. AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labelled definitely unrelated, definitely related, probably related, or possibly related to the study intervention.

For the purposes of this study, all SAEs will be required to be reported to the Committee, regardless of any judgment of their relatedness to the study. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, study condition, concomitant medications, the subject’s medical history and current conditions, and all relevant laboratory data. This will be provided annually at the DSMB committee meeting.

Reporting to site-specific IRBs will be done within 24 hours of the study team being made aware of the SAE. Reporting of any study-related SAEs and SAEs that severely impact participants (i.e., participant deaths) will be made to NIDA within 24-72 hours of the study team being made aware of the SAE.

Non-Serious Adverse Events. At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

Other Safety-Related Reports. At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.

Trial Efficacy

Plans for interim analysis for efficacy data.

If at any time during the course of the study, the Committee judges that risk to subjects outweighs the potential benefits or a safety concern arises, the Committee shall have the discretion and responsibility to recommend that the study be terminated. However, there are no pre-specified interim analysis for efficacy data given that (1) this is not an efficacy trial, rather a hybrid effectiveness-implementation trial; (2) the low anticipated risk of participation in the behavioral intervention and (3) small sample size. The power analysis is such that the full N would be required to make this determination. However, the DSMB will have the power to request analyses should they deem it necessary.

DSM Plan Administration

Responsibility for data safety and monitoring.

The principal investigator and primary mentor are ultimately responsible for data and safety monitoring. The processes described above ensure that the principal investigator will be aware of important study related issues on a regular basis. If any staff becomes aware that an adverse event occurs, this will immediately report it to the principal investigator and site project director. In addition, a yearly DSM committee review of all SAEs will occur.

To fulfil its mission of ensuring the safety and integrity of the study, it is necessary that the DSM Committee be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the

study. The DSMB members will function free of the career and financial interests of its members and will consist of three members with experience in conducting clinical intervention research for psychiatric and substance use disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues.

Frequency.

The DSM Committee will be updated annually with a report containing randomization data as well as adverse events. These adverse events are tracked for IRB submission as well. All SAEs are reported annually at continuing review. The DSM Committee will be comprised of nominees from both the Cape Town and US study sites.

Content of DSM report

The DSM report will include a tally and description of adverse events and serious adverse events. It will include a description of how these were handled, which experimental group the participant was assigned to (treatment or control), and if and how the participants' physician was notified. The DSM meeting will also involve a presentation from the P.I. regarding any emerging clinical issues involved in delivering the treatment, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year relevant to the trial, and any actions or changes with respect to the protocol. Sections of the DSM report will include:

A. Brief description of the trial
B. Baseline sociodemographic characteristics
C. Retention and disposition of study participants
D. Q.A. Issues
E. Regulatory Issues
F. AEs
G. SAEs
H. Efficacy

DSM Board Plan

Members. The Data and Safety Monitoring Board (DSMB) will function as an independent body charged with ensuring that the safety of study subjects is protected in Phase 3 and that the scientific goals of the study are being met. To support those purposes, the DSMB will review any proposed major amendments to the study protocol at the annual review, perform ongoing monitoring of drop-outs and all adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality. The DSM Committee will include both US- and South Africa-based investigators.

The Chairperson of the DSMB will communicate by e-mail and telephone conference with the other members. Reporting and communication about other matters will occur on a yearly basis, for the duration of Phase 3. Decisions of the DSMB will be made based on a majority vote of the members.

Conflict of interest. The DSMB members will function free of the career and financial interests of its members.

Protection of confidentiality. Adverse event reports and annual summaries will not include identifiable information. Each report will only include the participants' identification numbers.

Monitoring activities. At a minimum, the DSMB report includes an overview of the progress of participant intake and retention; summary reports describing participant compliance with visits, evaluations, and dosing as described in the protocol; a summary of all adverse events and major amendments to the protocol; and a summary of the completeness and quality

of key data elements needed to characterize participants, their dosing, and their primary and secondary outcomes. These reports are used by the DSM Committee to evaluate the capacity of the data capture and processing to support scientifically valid analyses. For ease of understanding, reports are done graphically, similarly to the CONSORT figures.

Communication plan to IRB and NIDA. The annual IRB Continuing Review will include the DSMB report for review. DSMB activity will be reported in annual NIH progress reports when applicable.

LIST OF MEASURES

A description of each measure can be found above in the outcomes section.

Table 1. **Measures at Major Assessments**

Measure	***Screening***	***Baseline***	***Post-Treatment***	***6- Month Follow-Up***
Demographics		X		
Mode of HIV Infection		X		
AUDIT		X	X	X
WHO-ASSIST	X		X	X
Substance Use History Questionnaire		X	X	X
Economics & RUQ		X	X	X
Sexual Risk-Taking Questions		X	X	X
ACTG- SF-21		X	X	X
Barriers to Adherence		X	X	X
Robbed, Recreational ARVs		X	X	X
Brief RCope		X	X	X
PHQ-9		X	X	X
PTQ		X	X	X
BADS		X	X	X
RPI		X	X	X
SOCRATES		X	X	X
SIP		X	X	X

PACS		X	X	X	
Interactive Toxicity Beliefs Questionnaire		X	X	X	
Ira Wilson's Three-Item Self-Report Measure		X	X	X	
Substance Use and HIV Related Stigma Scale (SU and HIV- SMS)		X	X	X	
Acceptability/Feasibility Questionnaire			X	X	
Urinalysis		X	X	X	
Blood Draw (DBS; CD4 count and viral load – when results not available in clinic records in past 3 months for baseline/ 30 days for follow-ups)		X	X	X	
Chart Extraction		X	X	X	
Wisepill		X	X		
Timeline Follow-Back		X	X	X	
Exit Interview (subset of intervention participants)				X	

Table 2. **List of Measures During Intervention**
(Participants randomized to intervention condition only)

Measure	***S1***	***S2***	***S3***	***S4***	***S5***	***S6***
SRA Weekly Adherence	X	X	X	X	X	X
Wisepill	X	X	X	X	X	X
Timeline Followback*	X*	X	X*	X	X	X
Urinalysis*			X*			

*Control participants will also be invited to the clinic for urinalysis and timeline follow-back approximately 5-weeks post-randomization (approximately equivalent in time to Session 3). Control participants will also do timeline follow-back at their randomization visit (corresponding to intervention participants' Session 1).

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