NCT04018391

Task Shifting to Treat Depression and HIV Medication Nonadherence in Low Resource Settings

Protocol

DETAILED PROTOCOL for TENDAI Trial

Section 1: Administrative information

1	**Project Title:**	**The TENDAI Trial: Task Shifting to Treat Depression and HIV Medication Nonadherence in Low Resource Settings**
2a	**Registration**	Study to be registered on ClinicalTrials.gov
3	**Protocol version**	8 May 2024 (Version 13.0)
4	**Funding**	R01 MH114708 awarded to Drs. Abas and O'Cleirigh by the National Institute of Mental Health (NIMH)
5a	**Roles and responsibilities**	**Melanie Abas**, M.D. (Principal Investigator), Kings College London – Created the protocol in the grant with Dr. O'Cleirigh, with feedback from Dr. Mangezi **Conall O'Cleirigh**, Ph.D. (Principal Investigator), Massachusetts General Hospital – Created the protocol in the grant with Dr. Abas, with feedback from Dr. Mangezi. **Walter Mangezi**, M.D. (Zimbabwe Site PI), University of Zimbabwe – Assisted Drs. Abas and O'Cleirigh in creating the protocol in the grant. King's College London will be the coordinating center for this study and will be covered by the IRB at King's College London. The intervention and all data collection will happen in Zimbabwe under the Joint Research Ethics Committee for the University of Zimbabwe College of Health Sciences and Parirenyatwa Group of Hospitals (JREC), Medical Research Council of Zimbabwe (MRCZ) and the Research Council of Zimbabwe (RCZ). Massachusetts General Hospital (MGH) will assist in data management, quality assurance, technical assistance to the site, and project management, covered by the MGH Partners IRB. The MGH team will develop and manage a HIPAA-compliant cloud-based data management system using REDCap, but study name files, consent forms, and other identifying information will be kept locally in Zimbabwe under their IRB regulations.
5b		King's College London The Strand London, UK WC2R 2LS

5c The Sponsor, King's College London, will be responsible for the initiation, ongoing management and financing of the trial. This includes ensuring all study sites have correct regulatory approvals including any amendments, and that all study staff have received human subjects and good clinical practice (GCP) training. The sponsor will also ensure the trial is conducted in accordance with the approved protocol and that systems are in place to report protocol deviations and adverse incidents. At the end of the study King's College London will be responsible for the dissemination of study findings and ensure data are retained and stored in line with regulatory approvals. King's College London will submit interim and final reports to the trial funder, NIH.

5d. Committees - General approach and meeting schedule: An organizational system for this study that is well-coordinated from a data management schedule has been developed. The overarching context for the data monitoring and management procedures is to maintain active, clear communication at each site and between sites. Specifically, Drs. Abas, O'Cleirigh, and Mangezi will hold weekly video meetings (via a service such as Skype, WebEx, or Zoom) with the site study staff including the Zimbabwe-based Programme Manager and the London based Project Manager, to direct study activities. This meeting schedule will be maintained throughout all years of the project. These meetings will address consistency of procedures, problems/challenges, and general training issues. For example, issues of data collection, budget, recruitment, data management and analysis will be addressed, training will be performed, and the protocol and assessment procedures will be reviewed on an ongoing basis. Agenda items that may involve the revealing of randomization condition will take place towards the end of the meeting, after study staff who are required to remain blinded (chiefly the Study Statisticians) have left. Any human subjects issues related to the ongoing work will also be discussed. In addition, the local Clinical Psychologist and the Research Coordinator will be involved in weekly supervision of adherence counsellors. These meetings will focus on supervision of intervention and assessment procedures. The London-based Programme Manager and MGH data manager will generate data related quality control reports—which will include information about data uploads from study tablets, issues with visit data that require follow-up and/or correction, and data corrections that have been made—to feed back to the sites to make any corrections in as close to real time as possible.

Multi PI Collaboration. Dr. Abas at KCL will have the primary responsibility for the oversight and administration of the study and the coordination of the study across sites. She will discharge these responsibilities in close collaboration with Dr. O'Cleirigh. Dr. Walter Mangezi will direct day-to-day operations on the ground and line manage the Zimbabwe Programme Manager. In the case of any disagreements between Dr. Mangezi(the site PI), and either of the two PIs, the other PI will break the tie. In the case of any disagreements between the PIs, Dr Dixon Chibanda, TENDAI study co-investigator, will break the tie.
Dr. Abas will chair the Trial Steering Committee and will bear the primary responsibility for maintaining communication between the sites, the consultants/collaborations, and NIH. Dr Abas and the KCL based Programme Manager will chair the Project Management Committee. Dr. O'Cleirigh will chair lead the Publications and Protocol Committee. These committees are described in more detail below.

Administrative Structure. An administrative structure is in place that ensures clear lines of communication, explicitly defined areas of responsibility, and an overall management structure for the administrative project. There will be weekly PI meetings (via Skype, WebEx, or Zoom) run by Dr. Abas with the site, including Dr. Dixon Chibanda and Dr. Mangezi as needed.

This will involve discussion of the study start up during the start-up phase, implementation during the implementation phase, and data analysis when data collection is complete.

The Trial Steering Committee comprised of the PIs, the co-Investigators, and consultants, will guide the overall management of the grant and will interact through 3-monthly meetings during start up, and additional contact as needed. These meetings will address issues of data collection, recruitment, intervention problems, human subjects; issues, the budget, and data management and analysis.

The Project Management Committee comprised of all key research staff working on the study will meet two-weekly to perform training and ongoing review of the implementation of the study. This meeting will comprise the main operations detail of the meeting, updates on 5trainings, recruitment, retention, eligibility and informed consent, and IRB issues. Data based reports on data collection, entry, and project management will also be presented and discussed at this meeting.

The Publications and Protocol Committee will facilitate and review all publications and presentations derived from data garnered in this grant in order to ensure its quality. Assignment of publications and other academic products of this project will be decided on by the publications committee, with lead roles equitably rotated between the three primary sites (Kings College London, MGH/Harvard, and the University of Zimbabwe). In the unlikely case that disagreements arise, the issue will be resolved by majority decision.

The site PI for this study will have the major responsibility for the management of the implementation of the study and directing the day-to-day operations. The site PI will be supported in this by the Project Management Committee. In addition, the site PI will receive local support, direction, and mentorship from other study staff through video calls and site visits.

Section 2: Introduction

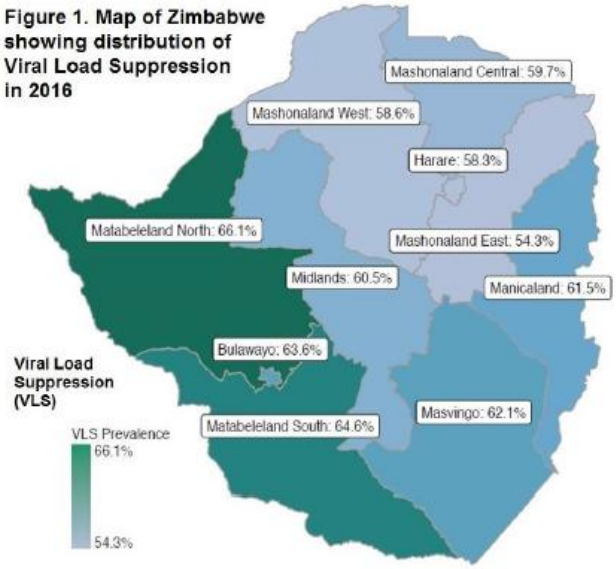
6a. Background and Rationale

a. Significance

Research on interventions for depression and poor adherence is pressing in the HIV-endemic countries of southern Africa, such as Zimbabwe. Firstly, this is because depression is highly prevalent in people living with HIV (PLWH) in this region, being associated world-wide with economic and educational disadvantage(1). Secondly, this is because depression is consistently associated with worse adherence to antiretroviral therapy (ART) (2, 3). Finally, this is because finding ways to help PLWH maintain adequate adherence on first and second-line ART regiments is critical, given the unaffordability of third-line regiments across most of the public care system.

Zimbabwe is a low-income country with the fifth highest HIV prevalence globally. Of its 16 million people, HIV prevalence in adults aged 15-64 is 14.6%. Prevalence reaches 29.8% for females aged 40-44 years and 28.7% for males aged 45-49 years (4). The incidence of new infections in adults is 0.59% in females and 0.31% in males (4). Zimbabwe's government is strongly committed to ending AIDS by 2030, as evidenced through national policies and programs such as 'Treat All' since 2016; decentralization of HIV care to primary care, district and provincial hospitals; roll-out of annual viral load testing; recent implementation of 'Test and Start'; and piloting of self-testing (5). Yet, according to the population HIV impact assessment (PHIA) survey, viral load suppression (VLS) at the population-level ranges from only 54%-66% (4). A key barrier to VLS is the low uptake of testing. For those who start ART, challenges include retention (29% of adults were lost to follow-up at 12 months) (6), poor adherence to ART, ART resistance, and limited options for ART regiments.

Depression and HIV are highly comorbid in Zimbabwe. In fact, depression in Zimbabwe is between 1.5 and two times as common among PLWH than those not infected,(7) as is the case internationally (8). Prevalence of depression in PLWH is Zimbabwe varies depending on sample, age, and location, but is at least 30% in those seeking general and primary health care (7, 9-13). In a random sample of 100 adults with detectable viral load in one ART clinic in Zimbabwe, 55% met criteria for significant depression (14). Being female, recent life events, poverty, intimate partner violence, and condomless sex are all strongly associated with depression in this setting (7, 15-17). In prior studies, barriers to taking ART in depressed Zimbabweans occurred in the context of poverty, poor education, unequal gender relations, stigma, and certain cultural and religious attitudes (18, 19).



Cognitive Behavioral Therapy (CBT) is an effective way to treat depression. Globally, Cognitive Behavioral Therapy (CBT) and antidepressant medications are treatments of choice for depression (20). Antidepressants are cheap but their use is limited by side-effects, poor adherence, and discontinuation relapse risk. On the other hand, CBT is effective and protects against relapse. However, CBT is complex and its efficacy relies on skilled psychological therapists not readily available in sub-Saharan Africa.

Due to a shortage of mental health professionals in Zimbabwe, interventions should be delivered with task-shifting. In sub-Saharan Africa, the median number of health professionals (1.7 per 100,000 population) (21) is less than one fiftieth the rate in the United States. Zimbabwe's national public health system, catering for 16 million, has only 12 psychiatrists and 3 clinical psychologists, nearly all based in the capital city. Mental health care in the provinces relies mainly on general nurses, lay counsellors, and some trained psychiatric nurses (22, 23). Task-shifting interventions, whereby identified tasks are given, under supervision, to non-specialist cadres, will thus be critical to scale-up any effective intervention (24).

Problem Solving Therapy (PST) may be an effective CBT intervention for depression in Zimbabwe. PST is a brief evidence-based CBT intervention for depression (25). Over the past decade, members of our team have pioneered a depression intervention based on simple empirically-supported PST (26). Systematic reviews confirm its efficacy in high income countries (27). PST is thought to work through enabling a more positive orientation towards resolving problems and by empowering people to have more adaptive coping skills and greater control over stressors. In PST, patients are taught a structured approach to identify problems and find workable solutions, geared at improving their ability to cope with stressful life experiences. PST is a promising and attractive option for low-resource settings because unlike traditional CBT, it does not require extensive training to complex skills (28). Furthermore, PST may be an ideal CBT intervention for this study's setting, as previous work has found that lay health workers can feasibly provide it under routine conditions. Through an RCT in Zimbabwe (n=560, of whom 220

were PLWH), this study's team demonstrated that PST leads to a meaningful improvement in depression compared to usual care (29). Therapy similar to PST was also effective for depression in low-income countries in post-conflict settings and after gender-based violence (30, 31). Furthermore, stepped care is an efficient use of scarce resources (32), for it incorporates principles to guide treatment choices (33). In Zimbabwe, the study team has embedded PST into a stepped care model, to create an intervention, stepped care for adherence (stepped care-AD). Initiated by Dr Abas, the TENDAI intervention will enhance PST through adding very basic behavioural activation in sessions 4 and 5, encouraging the person to identify positive, meaningful activities likely to bring joy and/or a sense of achievement. We are also enhancing through adding one session on coping with difficult emotional symptoms.

There is promising evidence supporting PST integrated with culturally adapted life-steps for adherence. Evidence from the US, including from systematic review data (34), is that treatment for depression using psychological therapy, integrated with the US-developed Life-Steps adherence intervention, based on CBT and on problem-solving principles, leads to improved adherence and/or viral suppression as well as improved depression (35) In a previous feasibility trial, PST for depression was integrated with 'Nzira Itsva', which translates as 'New Direction' and is a culturally-adapted version of Life-Steps (9). The combined intervention was called TENDAI (meaning 'thankful' in the Shona language). The study found that this task shifted for adherence (stepped care-AD) enabled depressed PLWH to generate and implement workable solutions to adherence barriers. This is the intervention that will be tested in this larger trial. It is worth noting that a large RCT of antidepressant therapy alone in PLWH with depression in the US found no significant effect on ART adherence despite good effects for depression (36).

Effectiveness trials can answer the question about whether an evidence-based intervention can work in real-world settings. Effectiveness trials with cost-effectiveness components help inform providers in practice, as well as policy-makers, as to whether the intervention can be used in particular settings (37), and can help translate efficacious interventions into actual practice (38). It is anticipated that evidence of a cost-effective intervention for depression and ART adherence in people with HIV will result in a more efficient allocation of resources in the health system, whereby health benefits are available to as many people as possible. The effective control of HIV with ART not only improves health outcomes, but is also important for cost containment. Adherence to first-line ART delays movement onto more expensive treatments (39), reduces the likelihood of onward transmission, and decreases the chances of the costly progression to AIDS (40). The issues around the cost implications of non-adherence will be examined.

b. Innovation

This will be the first trial in a low-income country of a stepped-care task-shifted model to achieve sustained viral suppression through treating depression and non-adherence in adults with HIV viremia and depression. The planned treatment is less resource-intensive and costly than traditional CBT, hitherto a key focus of treatment research on depression for PLWH. Any antidepressants used will be low-cost medications on the government-approved list. This study, an effectiveness trial, is attentive to the need to examine whether evidence-based interventions work in real-world settings.

The proposed study is attentive to cultural considerations. Problem-Solving Therapy (PST) has many features which have been found to appeal to low-income Zimbabweans who are mostly depression therapy naïve (9). These include the problem-solving focus, the face

credibility of the treatment, and the educational and problem-solving approach to symptom relief. The didactic and collaborative approach and the specific teaching of therapy skills demystify the process. PST is time-limited, present-oriented, and fits better with the lives of previous Zimbabwean participants who often confront poverty and traumatic life events. PST can be flexibly applied to multiple problems (depression, life stress, etc.). Furthermore, through formative work, PST and Life Steps for specific application in Zimbabwe has been culturally adapted. The PST strategies that comprise the treatment are consistent and achievable with the individuals' realities. For example, problem-solving has been adapted to include encouraging religious patients to use religious community supports (e.g., prayer, church attendance), consistent with the values of most patients in our pilot trials. Also, problem-solving has been adapted to encourage feasible income-generation activities.

This study has implications for treatment as prevention in an endemic setting. In 9 countries, HPTN052 demonstrated the efficacy of early ART to prevent HIV transmission (41). Analysis of those who started ART early revealed that depressive symptoms were the only psychosocial predictor of non-adherence (42). This intervention, specifically designed for those with detectable viral load and comorbid depression, addresses a group at heightened biological risk for HIV transmission and uncontrolled virus, with potential value for application in future Prep programs in resource-limited settings.

c. Preliminary studies

Zimbabwe-based preliminary studies. Through previous in-country programmatic work, the Life-Steps adherence program was adapted for implementation in Zimbabwe, integrated with a culturally adapted Problem-Solving Therapy, and a pilot randomized controlled trial was conducted to assess the program's feasibility, acceptability and potential for effect on depression, adherence, and viral suppression.

This current study's team previously translated the Patient Health Questionnaire (PHQ-9) into the Zimbabwean Shona and Ndebele languages. Then, in a primary care sample of 264 adults of whom 63% were PLWH, the PHQ-9 was validated against a diagnosis of major depression defined using the Structured Clinical Interview of the Diagnostic Statistical Manual (SCID) (10). A cut-off for PHQ-9 of $\geq$10, provided sensitivity of 91.28% ,specificity of 50.43%73.5% of cases correctly classified, and high reliability (Cronbach α=0.86) against a SCID diagnosis of depression.

The Life-Steps adherence intervention was also culturally adapted (43). Adaptation for the Zimbabwean context was informed through formative work, including analysis of 47 in-depth interviews with PLWH and health staff to gather data on local barriers to adherence (18). Modifications to Life-Steps included language, session length, tailoring of context for delivery by lay counselors, and inclusion of culturally-competent probes (44). The culturally adapted adherence intervention was called *Nzira Itsva*, which translates as New Direction. *Nzira Itsva* was tested in over 90 PLWH. It was found to be acceptable, feasible, and associated with improved adherence (44).

Through an open trial (n=9), the integration of a treatment for depression was described, based on Problem-Solving Therapy (PST), with adherence counseling (AD) using *Nzira Itsva*. It was called "PST-AD" and locally called TENDAI. This task-shifted stepped care intervention included six sessions of individual Problem-Solving Therapy for depression and adherence to ART delivered by an HIV counselor. For those whose depression did not respond, the intervention included the option of 2 levels of stepped care for depression: additional psychological therapy

(Step 2) and an antidepressant (Step 3), each provided by a more qualified cadre with supervision from a mental health clinician.

Next, a feasibility study using a pilot trial design was conducted. 32 participants (65% female) were randomized to either the stepped care-AD intervention or enhanced usual care (EUC). Acceptability of stepped care-AD was high for participants and adherence counselors, as demonstrated through qualitative interviews and 85% attendance to at least 5 of the 6 sessions. Participants receiving stepped care-AD saw significant improvements in depression on the PHQ-9 for depression, compared to EUC (PHQ-9; -4.7,95%CI: -8.2,-1.3, adjusted p=0.01). The study was not intended to be powered to detect statistically significant differences between the treatment arms, but more participants receiving stepped care-AD had a greater absolute increase in 90% adherence (25%) than in EUC (14%). Promising changes were seen in viral suppression (stepped care-AD arm 9/12 suppressed vs EUC arm 4/8 suppressed).

The study team previously provided preliminary evidence of an effect of PST on depression in PLWH in Zimbabwe from two pilot trials (45), and recently completed a cluster RCT of PST in general primary care clinic attenders in Zimbabwe delivered by trained non-specialists (46). Of the 563 participants, 283 (42%) were PLWH; the prevalence of depression after 6 months in PLWH was 21% in the intervention arm compared to 46% in the control group (prevalence ratio=0.43; 95%CI 0.26, 0.70).

US-based preliminary studies. The U.S. investigators completed two of the first U.S. trials of adherence interventions for HIV (43, 47) and developed the first adherence and depression treatment, Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD), that comprises Problem-Solving Therapy and the adherence treatment component of Life-Steps, on which the current study is based.

A pilot efficacy trial (48) of CBT-AD showed, in a cross-over design, that patients in HIV care (N=43) with HIV and clinical depression who were initially randomized to CBT-AD had better improvements in electronically measured adherence and depression (independent assessor with Hamilton Rating Scale and CGI) than those who received enhanced treatment as usual (ETAU). These gains were maintained at 12 months. Viral load also improved significantly for those receiving the intervention.

An efficacy trial in substance users , an RCT (N=89), compared CBT-AD to enhanced treatment as usual (ETAU). HIV-positive patients with IDU histories who had a clinical diagnosis of depression were enrolled. Those receiving the treatment had better adherence and improved depression (independently assessed) than those in ETAU. The results were maintained for depression at 12 months, and the adherence gains were maintained at follow-up for those who did not experience substance use relapse (49). Treatment-related changes in adherence were mediated by treatment-related changes in depression (50), providing support for this study's conceptual model (Figure 2).

A full-scale efficacy trial, a three-arm trial (CBT-AD, ETAU, and informational/supportive psychotherapy integrated with adherence counseling), was conducted to test CBT-AD in HIV care. Findings demonstrated that CBT-AD was superior to ETAU in MEMS-based adherence and depression after treatment discontinuation, and that these differences were maintained over follow-up.

In short, CBT-AD has generally been a successful approach to treating depression and improving adherence. CBT is the most studied and efficacious psychosocial treatment for

depression, and the track record is strong of integrating CBT for depression with adherence counseling (CBT-AD) in PLWH. Given these facts, and given the high rates of depression, nonadherence, and treatment failure in the Zimbabwean population, TENDAI, which uses task shifting to implement stepped care for adherence and depression, includes PST,a simpler cognitive behavioral intervention and is thus highly relevant and of high public health impact.

6b. Choice of comparators: The stepped care-AD intervention will be compared to Enhanced Usual Care (EUC). Those randomized to the EUC will receive standard of care (three clinic-provided adherence counseling sessions) and a letter to their usual care provider alerting them to their patient's depression. See section 11a.

7. Objectives (also see Outcomes Section 12)

The overarching aim of this study is to test the effectiveness and cost-effectiveness of an intervention (stepped care-AD), systematically pretested through a prior feasibility and acceptability trial. The intervention targets poor ART adherence and depression. The aims will be achieved by randomizing 290 participants attending ART clinics in Mashonaland East, Zimbabwe, to either stepped care-AD or Enhanced Usual Care (EUC). Specifically, the aims of this study are:

Primary Objective

To evaluate the effectiveness of the task-shifted stepped care-AD intervention on viral suppression compared at 12-months post-randomization follow-up in comparison with EUC.

Secondary Objectives

To evaluate the effectiveness, in the intervention arm compared with Enhanced Usual Care (EUC), of;

1. The stepped care-AD intervention on depression at 12 months post-randomization.
2. The stepped care-AD intervention on adherence at 4, 8 and 12 months post-randomization.
3. The stepped care-AD intervention of viral load (continuous measure in copies/mL) at 12 months.

Tertiary objectives

1. To estimate the cost effectiveness of the task-shifted stepped care-AD intervention on viral suppression and quality of life at 12-months.

We will also address a few exploratory questions (see Section 12 Outcomes).

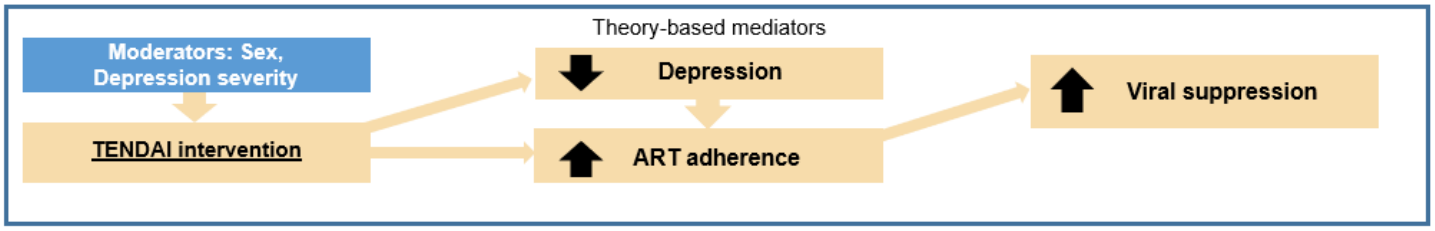
8. Trial Design

Overview. The proposed project is a 2-arm parallel group superiority 1:1 randomized effectiveness trial (n=290) evaluating the effectiveness and cost-effectiveness of a brief, stepped-care treatment (stepped care-AD) for depression and ART adherence in viremic patients with HIV. The primary outcome is viral suppression, with medication adherence, and depression as key secondary outcomes and cost-effectiveness a tertiary outcome. The trial intervention prioritizes task-shifting using adherence counselors and nurses as interventionists.

Our stepped-care approach utilizes two successive intensity levels of depression treatment for non-responders to maximize efficient use of resources in resource limited settings. As an effectiveness trial, the comparison arm is enhanced usual care.

Conceptual Model. The stepped care-AD intervention is designed to have a significant impact on viral suppression by producing clinically significant reduction in depressive symptoms and increase ART adherence through engagement in HIV care. We hypothesize direct intervention effects on depression and ART adherence, and indirect effects on HIV viral suppression through improvements in adherence. Both components of problem solving therapy for depression and adherence (Enhanced Problem-Solving Therapy and Life Steps) are a skills-based approach to behavior change. Therapy begins with selecting motivated goals for behavior change, identifying barriers to meeting these goals, and developing solutions and strategies to overcome these barriers. This approach is consistent with Social-Cognitive Theory (51) and its application to HIV related research (49). We will assess moderators of any treatment effect to identify those groups who benefit most. The conceptual model of the stepped care-AD intervention is illustrated in Figure 2 below.

Figure 2: Conceptual Model of the TENDAI Intervention



Our model for measuring cost-effectiveness is based off of the Agency for Healthcare Research and Quality's (AHRQ) seven criteria (52), and Singal et al's (37) five criteria, for distinguishing effectiveness from efficacy trials. The ways in which our proposed project is in compliance with effectiveness recommendations is shown in Table 1 to the side.

Table 1: Effectiveness Recommendations

AHRQ Recommendations for Effectiveness Trials.	**Current Study Compliance with Effectiveness Recommendations**
1 ***Population in Primary Care or Real-World Setting***	The sample comprises patients with detectable viral load and depression in HIV primary care and general secondary care provincial settings.
2 ***Less Stringent Eligibility Criteria***	Participants will be selected based only on outcomes of highest clinical and public health significance with limited exclusion criteria.
3 ***Health Outcomes focus***	Primary Study Outcome: percent virally suppressed.
4 ***Long Study Duration/ Clinically Relevant Treatment Modalities***	The treatments are the most basic and clinically relevant for the problems of adherence and depression, and participants will be followed for 1 year.
5 ***Adequate Sample Size to assess a minimally important difference***	Our prior work has shown clinically relevant decreases in depression and increases in adherence, and the present study is powered to detect these improvements.
6 ***Intent to Treat (ITT) Analysis***	ITT analyses are specified in the grant and all participants are included regardless of whether they completed the study or not.
7 ***Representative Usual Providers***	Use of adherence counselors as interventionists and other procedures to support fidelity to the treatment as well as sustainability.
8 ***Concurrent interventions permitted***	We will not restrict concurrent treatment; we incorporate stepped care for non-responders, and facilitate referrals to treatment
9 ***Applied with flexibility***	The intervention allows for individualizing the treatment to the needs of each participant (i.e. empowering them to implement solutions to their own unique adherence barriers) as in prior efficacy trials.[37,53]

Subjects will be 290 HIV-positive men and women ≥18 years, resident in the province of Mashonaland East in Zimbabwe and attending one or more study sites which are ART clinics at hospitals in the province. They will have been screened positive for depression (using the Patient Health Questionnaire (PHQ-9) with a cut off of greater or equal to 10), have been initiated on ART for ≥ 6 months and have a detectable viral load in the two months prior to recruitment, as per national standard (>1000 copies/mL). Full inclusion/exclusion criteria may be

found in Section 10. Subjects must be able to give informed consent and be able to understand and adhere to study procedures (e.g., complete assessment battery, meet with a study interventionist). Participants will also be asked to sign a release of medical information authorizing study personnel access to their medical record for the duration of the study to access HIV treatment information only (i.e., ART regimen and any changes in this, CD4, missed HIV care appointments, and viral load assay results).

At each study site, the research assistants and study nurses will coordinate subject recruitment. Potential participants with detectable viral load will be approached when they attend the clinic for the result of their first (6 month) or annual viral load test. We will also approach clinic patients at high risk of having a detectable viral load (e.g. PLWHIV with missed appointments, or who have defaulted medication, or who self-report adherence problems) but who have not had a blood test in the last 2 months and seek consent for screening them with a viral load test. Interested potential participants will first speak with the research assistant/research nurse or another study staff member in person to do a brief initial screen.

This initial screen will include the PHQ-2, a two-item measure of the PHQ-9, and will also assess participants age, viral load results in past 2 months, time on ART and risk of having a detectable viral load. If preliminary criteria are met, participants will then complete the informed consent process, and baseline measure comprising a self-report psychosocial assessment battery and interview-administered measures, including a MINI psychiatric diagnostic assessment, and measures for the economic evaluation and quality of life (Client Services Receipt Inventory, and EQ-5D-3L) (detailed in section 18a). For participants who have not had a blood test in the last 2 months, a viral load test will also be performed for eligibility screening at baseline, after informed consent has been obtained and baseline measures have been completed. The consent process will include consent to study procedures, consent to release of information from their medical record regarding HIV disease status and treatment, and consent to share results of study assessments with their treatment team.

Participants will be randomized approximately two weeks from their baseline assessment. Randomization will occur only once the Site PI (Dr Mangezi), Clinical Psychologist, Zimbabwe Programme Manager and recruiting Research Assistant have met to discuss eligibility including ensuring viral load results have been received. This meeting will occur weekly. Within this time between the first study visit and the randomization study visit participants will have sufficient time to meet with their provider and receive usual care treatment for mood disorders. The provider will not be limited in any way to follow what he or she would normally do for someone with these comorbid conditions (e.g. World Health Organization Mental Health GAP (mhGAP) guidelines, Zimbabwe Essential Drug List prescribing guidelines for treatment with antidepressants).

At the randomization visit participants will be asked to provide blood via venipuncture. From this a few drops of blood for detection of ART drugs, using Dried Blood Spot (DBS) will be prepared. The DBS samples will be stored and shipped to the University of Cape Town South Africa for analysis. Participants will be informed of the results of their psychosocial assessments including the results of mental health diagnostic assessment (the MINI). For those who consent for that information to be shared with their treatment team a letter will be sent to the treatment provider/team documenting the mental health conditions for which they meet diagnostic criteria. The participant’s treatment team will also be informed that participants who are receiving concomitant psychopharmacological treatment for mood disorders continue to be eligible to participate in the study.

Those assigned to the experimental condition (stepped care-AD) will have 6 sessions of the intervention focused on improving depression and adherence, plus one booster 12 weeks post randomization. Those assigned to the Enhanced Usual Care arm will be offered adherence counselling (3 sessions) as would normally be delivered by adherence counsellors in response to someone with a detectable viral load, according to the Zimbabwe Ministry of Health Operational and Service Delivery Manual for the Prevention, Care and Treatment of HIV in Zimbabwe. We will enhance usual care for depression in the control condition in 3 ways. First, we will provide training on depression management (WHO Mental Health Gap intervention guide (mhGAP)) to all health providers in the study clinic sites. Second, we will provide a letter informing participants' HIV health provider of their diagnosis of depression. Third, we will offer the stepped care-AD intervention, cost free, to all control arm participants once their study participation is complete. These are detailed further in section 11a.

All participants will have a post-treatment assessment approximately 4-months post-randomization, a second follow-up assessment at 8-months post-randomization, and a final follow up 12-months post-randomization. At each post-randomization assessment, an independent assessor, who is blind to study condition, will administer the PHQ-9 for symptoms of depression. Participants will repeat the self-report psychosocial assessment battery gathered to address secondary, tertiary and exploratory objectives (see Section 12 Outcomes and Table 18a). Dried blood spots will be collected at each follow up visit for the detection of ART drugs, to measure ART adherence. At the final 12-month follow-up, we will also extract chart information from medical records for pharmacy refill data and HIV viral load results. Clients whose medical records do not show results of a viral load test in the past 30 days will be invited to undergo venipuncture for viral load testing which will be in addition to the venipuncture for ART detection.

Payment of the trial participants in line with local standards (Medical Research Council of Zimbabwe) will be given for research assessments at baseline, and at 4, 8 and 12-months post randomization. In addition, payment to participants receiving the intervention will be given in line with local standards for providing data for stepped care-AD session visits. Although those in the enhanced usual care arm will have fewer scheduled clinical sessions, the same total amount will be provided to participants in both arms. Strategies to maximize retention will include sending text message reminders to participants the day before scheduled appointments and collecting extensive locator information (e.g., contact information of two significant others with whom the participant is in regular contact, involvement with HIV service organizations). We will make efforts to maintain contact with individuals who move to a non-study site for their HIV care and are still willing to complete follow-up. We will aim to complete outcome assessments with all participants whether they attend clinical session visits or not.

Section 3a: Methods—participants, interventions, and outcomes

9. **Study setting.** The study will take place at Marondera Provincial Hospital (semi-urban). Marondera is a town surrounded by farming areas, with some commercial farms and light industry. Marondera Provincial Hospital (general secondary care) has 4639 adult patients on ART with 124 new initiations per month.; We will also screen and recruit from Nyameni and Dombotombo clinics which are part of the city of Marondera. Patients from these clinics will be referred to Marondera Provincial Hospital to enable them to attend the research visits. The study is ardently supported by the Ministry of Health, who encouraged us to conduct the trial in this province to support the development of sustainable treatment models in semi-urban and rural health facilities.

To meet our recruitment target, a second study site will open at Chitungwiza Central Hospital. Chitungwiza Central Hospital is located in Chitungwiza town which is approximately 70km from Marondera town and 25km from Harare the capital city. We will also screen and recruit from Chitungwiza Municipality clinics (Seke South Clinic, Seke North Clinic, Zengeza Clinic and St Mary's Clinic) which are in Chitungwiza. Chitungwiza is one of the largest high density towns in Zimbabwe and it is divided into 5 townships namely St Marys, Zengeza, Seke, Manyame and Rockview. Chitungwiza has several home industries and few a few light to heavy industries.

Catchment areas for Chitungwiza central hospital include Chitungwiza town, the Mash East province, nearby farms and Epworth. Chitungwiza Central Hospital therefore serves both urban and rural population as it is also surrounded by rural communities such as Dema, Seke, Mayambara and Manyame rural district. There are approximately 5300 adult patients receiving HIV treatment at Chitungwiza Central hospital. We will also recruit participants from Kunaka Hospital (Dema), Beatrice District Hospital and Mahusekwa. Patients from these clinics may be referred to Chitungwiza Central Hospital to enable them to attend the research visits.
Study participants. Study participants will be 290 patients at the ART clinics at Marondera Hospital and Chitungwiza Central Hospital in Zimbabwe who have had a detectable viral load (>1000 copies/mL) in the past 2 months, either following routine testing or from obtaining venous blood for viral load testing for high risk groups with no recent clinic viral load (e.g. PLWH with missed appointments, those who have 'defaulted' medication, or those who self-report adherence problems). In terms of routine testing, the National Strategy allows for routine viral load (VL) testing six months after ART initiation. Those who are suppressed (currently defined as VL<1000 copies/mL) have an annual blood test thereafter. Those with a detectable viral load (>1000 copies/mL) six months after initiation, or from routine annual tests, or because of being tested for clinical indication, receive adherence counselling, and a repeat VL after three months. We expect that approximately 60% of participants will be female.

10. Eligibility Criteria

Inclusion criteria. Baseline inclusion criteria for this study include:
1) Initiated on ART for at least 6 months
2) Clinically significant depression symptoms (scoring $\geq$10 on the Patient Health Questionnaire-9)
3) Viral non-suppression in past two months per local clinical standard (VL>1000 copies/mL) assessed through local clinic testing or study procedure testing
4) Able to provide informed consent (including being willing for the study team to access medical records for the purpose of this protocol)
5) If prescribed antidepressants, on a stable regimen and dose for at least 2 months

Exclusion criteria. Exclusion criteria include:
1) Unable to provide informed consent
2) Active major mental illness (e.g. untreated psychosis or mania, actively suicidal), major untreated or undertreated mental illness or advanced physical disease or severe cognitive impairment (assessed using the psychosis module of the MINI, the PHQ-9, and the International HIV dementia Scale) which would interfere with engagement in PST-AD
3) Has ever already received PST or CBT for depression
4) Less than 18 years of age

The inclusion and exclusion criteria were chosen to balance methodological rigor/internal validity with effectiveness – the ability to have results be as generalizable as possible.

Accordingly, we are not excluding individuals with comorbid alcohol or other substance use disorders, or additional mental health comorbidity, except for active major mental illness such as psychosis or severe cognitive impairment. To maximize the impact of the intervention, we are including those meeting the local standards for detectable viral load (currently>1000 copies/mL) and who screen above the cut-point on the validated PHQ-9 for depression. These individuals will be at highest risk for ongoing adherence-based treatment failure (53).

Based on patient census numbers provided by the Ministry of Health, we anticipate over 10,100 patients on ART during the study accrual period (2.25 years). Based on national and our own pilot data, we expect 17% of this number to have viral non-suppression (n=1717) and for 50% of those to score ≥ 10 on the Patient Health Questionnaire (PHQ-9) screening for test depression (n=859) and not to meet exclusion criteria. Assuming 70% of qualifying participants consent to enroll (n=600), we will have sufficient numbers to recruit the sample in 2.25 years as planned (~10 patients per month).

11a. Interventions

Control Group – Enhanced Usual Care (EUC). Those randomized into EUC will have clinic-provided adherence counseling provided as part of usual care for non-suppressed viral load (54), delivered individually by an adherence counselor or nurse based at the health care facility. The adherence counsellor or nurse will not have received training in the stepped care-AD intervention. In this adherence counseling, three sessions are standard. The session covers (a) establishing the client's level of knowledge about HIV and ART, (b) providing information about use of ART and encouraging the client to be adherent, and (c) getting the client to describe any problems and barriers including stress and depression. The strategies are: use of a treatment supporter; use of an alarm (e.g. on a mobile phone); linking ART taking to daily routines; disclosure; referral to a support group; referral to an NGO for economic support; provision of general psychological support; and referral to a clinician. Although there is an awareness that depression can impact adherence, screening for depression using a questionnaire or mental state assessment is not currently routine practice in any government facility.

Usual care for depression will be enhanced for this study in three ways:

1. First, the study team will provide training in depression management to all health service providers in the study clinic sites, using the second version of the World Health Organization (WHO) *Mental Health Gap intervention guide (mhGAP) (55)*. The WHO produced mhGAP from a synthesis of systematic reviews, aimed at general nurses and doctors. Study staff will follow the same teaching protocol used by WHO, which has already been followed for primary care clinics in the capital city Harare. This includes core psychoeducation messages for health staff to give to the patient and their carers about reducing stress, strengthening social support, and benefits of increasing functioning in their daily activities and community life. It covers how to commence and maintain anti-depressants, specifically fluoxetine, for 9 to 12 months after resolution of symptoms. The WHO mhGAP program is being rolled out across numerous low income countries.
2. Second, we will provide a letter for each participant communicating diagnosis of depression to their HIV-care provider.
3. Third we will provide no-cost treatment of the intervention components to each participant in the control condition who wants it when they have completed their 12 month follow up assessment.

These three enhancements of usual care will be supported by the increasing availability more generally of antidepressants in general health care. Also, awareness of depression treatment is increasing in in Zimbabwe, following the rollout of the Friendship Bench, a lay-health worker delivered stepped-care program for depression in three cities.

Intervention Group - Stepped Care-AD. Those randomized into stepped care-AD will receive problem solving therapy for adherence and depression (PST-AD) over 6-weekly sessions, delivered by adherence counselors. The stepped care-AD will be delivered by adherence counsellors specifically trained in the intervention, who do not provide routine care and will take place in a separate building to the EUC counselling. This is to reduce the risk of contamination between the two arms, by increasing the privacy of the stepped care-AD intervention sessions, and preventing awareness of the stepped care-AD intervention impacting the counselling the EUC participants receive. Participants will be considered to have completed the intervention after finishing 4 or more sessions. To reduce participant attrition, sessions 4, 5 and 6 may be conducted by telephone for participants who are unable to travel to the clinic (for example if participants cannot travel to the clinic because of C-19 lockdown travel restriction). The 6 TENDAI sessions are as follows:

Session 1 (50 minutes): This session is dedicated to *Nzira Itsva,* the culturally and linguistically adapted Life-Steps adherence intervention (43, 44, 56). It has educational, motivational, and problem-solving components. The education component is delivered through video and subsequent guided dialogue. This component was culturally adapted through consultation with local providers and Zimbabwean researchers and translated into the Shona language. A client's personal motivation for good adherence is elicited through discussion, and personal barriers to adherence are identified using a checklist. Participants learn problem-solving strategies around their own barriers to adherence, which commonly include difficulties attending appointments due to constrained finances or lack of autonomy at work or at home; difficulties asking questions of the medical team; having a regular pill-taking schedule, and for women, the ways their male partner may interfere with pill-taking (44). The first session is operationalized with a review of daily adherence data over the past two weeks generated by self report adherence timeline follow back.

Session 2-4 (50 minutes): This session follows classical PST for depression, including psycho-education about depression; eliciting, listing and reflecting back to the client their problems; helping them select one problem from the list to focus on; brainstorming solutions; rating them according to importance and feasibility; choosing a solution; and making a plan to implement it over the next week (57). The session starts with '*kuvhura pfungwa* ('opening up the mind'), which includes psychoeducation and normalizing depression as a mental health condition. The aim is to identify and formulate the nature of problems experienced that could contribute to depressed mood. Clients categorize and rate each problem in terms of its importance and potential solvability, which supports them taking control of their problems and determines what is important to them. Then clients and counselors brainstorm lists of possible solutions. In the next stage, *kusimudzira* ('encouraging'), Clients categorize and rate each problem in terms of its importance and potential solvability, which supports them taking control of their problems and determines what is important to them. Then clients and counselors brainstorm lists of possible solutions. In the next stage, *kusimbisa* ('strengthening'), clients are encouraged to consider the pros and cons of potential solutions (29). The counselor helps them recognize potentially dysfunctional problem-solving style activities and helps them develop a SMART (specific, measurable, achievable, realistic and timely) plan for the successful resolution of specific problems. In the final stage Kusimbisisa ('further strengthening'), participants are reassured and encouraged that the goals they set can be achieved. Negative attitudes or beliefs

which may interfere with implementing the action plan are discouraged. During the session, 10-15 minutes are spent reviewing ART adherence, the client's progress in resolving the barriers to adherence identified in session one, and, as needed, problem-solving over additional adherence barriers. The PHQ-9 adapted to a 1-week response, will be administered in Session 3-6 to monitor progress on depressive symptomology. Participants will be asked to complete the PHQ-9 at sessions 3-5 alone or with the help of the Research mental health nurses.

Sessions 5&6 (50 minutes each): The final two sessions involve evaluating progress and will focus primarily on pleasant activity scheduling as an additional strategy for coping with depressive symptoms. This session may also include generating new solutions and tackling different problems. Each session includes approximately 10 minutes on adherence barriers and 15 minutes on depression problems. The research mental health nurses re-administer the PHQ-9 screening scale for depression to evaluate need to step up to next level of care.

Booster Session (50 minutes): Approximately 12 weeks post-randomization, participants in the intervention will have a booster session. This purpose of this visit will be to check in regarding maintenance of treatment goals and progress. The first half of the session will be used to discuss current depressive symptoms as well as adherence to HIV treatment and antidepressant medications (for those who have been stepped up to this level of care) since the end of treatment. The second half of the session will be used to make a plan for ongoing activity scheduling to facilitate coping with depressive symptoms. The research mental health nurses re-administer the PHQ-9 screening scale for depression to evaluate need to step up to next level of care.

Fidelity of the Treatment/Training and Clinical Supervision. Fidelity of the intervention and counsellor competence will be assessed via review and scoring of audio recordings of PST-AD sessions, expanding on a processes we tested in our R21 (14). All therapy and assessment sessions will be recorded and 10% of the sessions will be transcribed, translated and scored for fidelity to the protocol and for counsellor competencies. This will be achieved through the development of a standardized tool. The inter-rater reliability of the tool will be established through a pilot of the tool, with expert clinicians scoring the transcribed and translated transcripts. Data based feedback on fidelity and competence will be provided to study counsellors during weekly clinical supervision meetings facilitated by the study psychologist. The Adherence Counsellors and the RMN will be trained on the treatment and the delivery of the full stepped care intervention. Training will be provided by the Dr O'Cleirigh, Dr Abas and Dr Mangezi. The counsellors and nurses will be trained to set criteria using didactic instruction, video tape review, role plays, and feedback. Weekly clinical supervision from the Clinical Psychologist and Dr Mangezi will support ongoing training and skill development. Initial training and ongoing support will also be used to ensure counselors delivering the stepped care-AD intervention use a separate private room or cabin, and do not peer-train the health care facility adherence counsellors delivering usual care to avoid contamination between arms.

11b. Stepped Care Treatment Protocol. Step 1 to treat depression in intervention participants is PST-AD. However, the PHQ-9, adapted to a 1-week response, will be re-administered in Sessions 3, 4, 5, 6 and Booster to test if participants' depression is responding to the treatment. From session 4 if the participants' depression does not respond (PHQ-9 >=10 at session 4, 5,6 or booster), or if they have less than a 5-point improvement in PHQ-9 score, they will be stepped up to next level care (58).

Step 2: Session 4, 5 and 6 assessment for antidepressant treatment. If the depression score continues above cut-off (PHQ-9 >=10) or if they have less than a 5-point improvement in PHQ-9 score from Session 4, the Research Mental Health Nurse will do a psychopharmacological assessment to prescribe an antidepressant (fluoxetine) to augment PST-AD. Although antidepressants have not been routinely available in HIV clinics in Zimbabwe, the Ministry of Health has facilitated Psychiatric Nurses, who are available in many hospitals nationwide, to be trained to dispense psychotropic medications, and fluoxetine is on the National Essential Drugs list. The research mental health nurse will work under the supervision of the Site PI who is a psychiatrist.

12. Outcomes

Primary outcome measures

1. The proportion of participants who achieved viral suppression (defined as <1000 copies/mL) at 12-months post-randomization follow-up.

Secondary outcomes measures

1. Depression at 12 months post randomization measured as the total score on the Patient Health Questionnaire (PHQ-9).
2. Adherence to ART medication at 4, 8 and 12 months post randomization assessed as the proportion of the sample achieving at least 90% adherence in the past month assessed through pharmacy refill.
3. Self-reported adherence to ART medication at 4, 8, and 12-months post randomization assessed as the frequency of adherence in the past 30 days.
4. Viral load copies/mL at 12-months post-randomization follow-up measured as Mean log Viral Load.

Tertiary outcomes measures

1. The cost-effectiveness of the task-shifted stepped care-AD intervention on viral suppression (dichotomous outcome) and quality of life at 12-months. Costs will be measured using the Client Services Receipt Inventory from data collected in interview and from clinical records and quality of life using the modified EQ-5D-3L based on the Shona dialect of the research site.

Exploratory outcome measures

1. Exploratory mediators of treatment effects on depression and adherence will be explored using a locally-developed social support measure (59), Adherence Self-Efficacy Scale, and Social Problem Solving Self-Efficacy and Skills.
2. Exploratory mediators of treatment effects on viral suppression will explored using PHQ-9 for depression and adherence. We will initially explore each of self-report, pharmacy refill, and DBS measures of adherence as potential mediators, then also a composite measure of adherence using all three as indicators of an adherence latent variable in line with established procedures (60).

3. Sex, depression severity and household assets, will be tested as moderators of the treatment effect on viral suppression, adherence, and depression.

13. Participant timeline

Study procedures. We plan to complete start up during the first 9 months of the study. Using the stepped care-AD intervention manual and training protocol informed by a prior feasibility and acceptability grant, adherence counselors, nurses, and other study staff will be hired and trained during this period. All health providers at both sites will be trained in the World Health Organization mental health gap intervention guidelines for depression.

Figure 3. Overview of study design

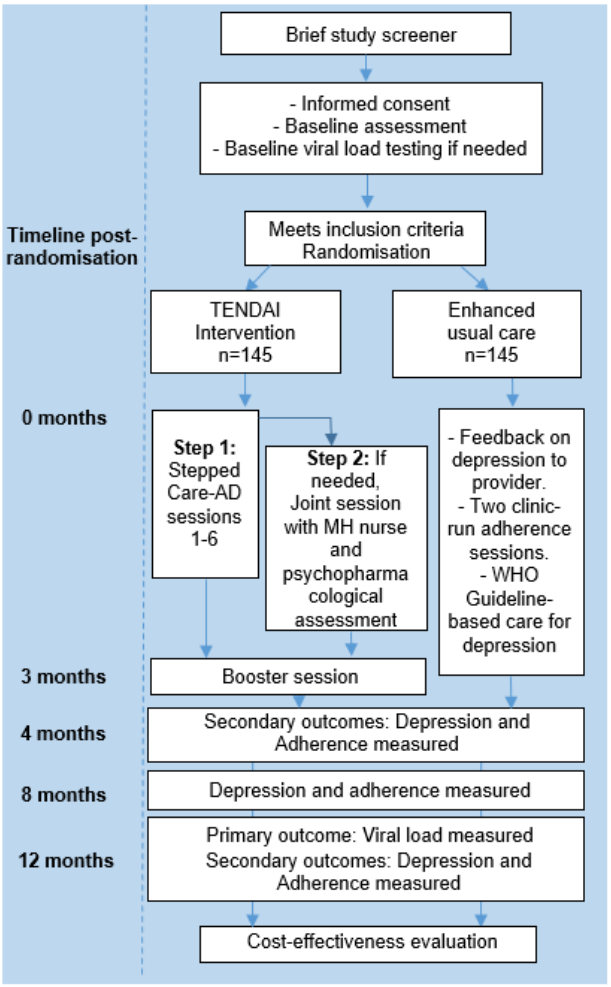


Figure 3 shows the overview of the study design. Participants will complete a brief study screener before informed consent. This will ensure participants meet age and HIV treatment inclusion criteria. The initial screen will also include the PHQ-2, a two-item measure of the PHQ-9 to assess depression, as a 'first step' approach using a cut off score of >=2. This will allow the study to exclude participants who will not meet inclusion criteria before all eligibility criteria are assessed after informed consent at baseline.

At first study visit participants complete the informed consent process and baseline measures to determine full eligibility. The baseline measures include time on ART, viral load, and assessments of major active mental disorder, depression, advanced physical disease or severe cognitive impairment to determine if a participant meets all inclusion or any exclusion criteria. As part of the enhancement of usual care (EUC), letters will be sent to each participant's HIV-care provider documenting their depression and stating that study participation should not interfere with any other treatment they might prescribe. Approximately two weeks after baseline, participants will come back for a randomization visit. Those randomized to the stepped care-AD intervention will receive 6 individual intervention sessions provided over six weeks, followed by one booster session 12-weeks post-randomization. Those randomized into the EUC condition will receive the standard of care (clinic provided adherence counseling sessions). The post-treatment assessment will occur 4-months post- randomization, and two more follow-up assessments will follow (one at 8-months post-randomization, and the next at 12-months post-randomization).

Baseline study visit. Upon meeting inclusion criteria and the informed consent process, eligible and still-interested participants will begin their baseline assessment. As part of their baseline assessment, participants will be assessed using the PHQ-9, a self-report measure covering symptoms experienced over the past two weeks.

In the baseline assessment, participants will also complete a self-report battery with the research assistant comprising of demographics, HIV and treatment information, self-report adherence, social support, use of health services, barriers to adherence, use of alcohol and substances, and overall health information (see section 18a). For those who screened positive for depression and are at high risk of viral non-suppression but who have not had this confirmed by blood test in the last 2 months, baseline assessment will include providing blood via venipuncture for a viral load test to ensure eligibility.

The interventionist will complete the clinically relevant psychosocial assessments at baseline. This includes the Mini International Interview (MINI) (61, 62), a psychiatric diagnostic assessment to evaluate study inclusion/exclusion criteria. The US-based investigators have extensive experience using the MINI in clinical trials and will conduct weekly supervision meetings to review audio recordings of live patient interviews to ensure assessment reliability among the team. The interventionist will also complete the PCL-5 (63) posttraumatic stress disorder checklist. The staff administering questionnaires and collecting other data must ensure all baseline data are complete before proceeding with randomization. The study team (Site PI, research assistant, interventionist and clinical psychologist) will meet to discuss whether the participant meets entry criteria, led by the clinical psychologist, before randomization. The researcher will also communicate with the participant's HIV care clinician regarding the diagnosis of depression in the form of a letter. The provider will have the option to start anti-depressant medication or provide other care / referrals as needed.

Randomization visit. Approximately two weeks after the initial baseline assessment, participants will return for their randomization visit. At this visit, participants will be randomly assigned to either stepped care-AD or EUC and will also have venipuncture to provide a blood spot (DBS) for presence of any of the ART drugs used in Zimbabwe. Consideration was given to stratify randomization based upon current antidepressant use or alcohol or substance use disorders. However, it is expected that less than 4% of the sample will be prescribed antidepressants (14), and the documentation of alcohol or substance use disorders as influencing psychosocial treatment effects in Zimbabwe is absent from the research record, so we will not stratify randomization on these factors. Data Safety Monitoring Board (DSMB) reports will include information allowing assessment of balance of these variables between the two groups.

Eligible participants will be randomly assigned to receive either the stepped care-AD intervention or EUC. Participants will be randomly assigned in a 1:1 ratio using a block randomization procedure coordinated in collaboration with REDCap.

Follow-up visits. Follow-up assessments will occur at 4-, 8-, and 12-months post-randomization. For all follow-up assessments, an independent assessor, blind to study condition, will conduct the PHQ-9, EQ-5D-3L, and self report adherence measures in order to minimize bias. Research assistants will complete the rest of the battery of measures (see section 18a). Follow up visits will be conducted within a window of one month before and two months after each time point, up to 16 months post randomization, but outcome data will still be collected outside the window where necessary.

The 4, 8 and 12 month follow-up visits will allow for an assessment of treatment-related effects on depression and ART adherence at three time points post-treatment, and for identification of participants in both the stepped care-AD and EUC conditions who have started antidepressant medication. Study participants will complete the psychosocial assessment and self-report questionnaires at each of the study follow-ups at 4, 8 and 12 months. Adherence will also be

assessed using Pharmacy Refill count methodology to determine the proportion of days covered for each participant during the follow-up period and DBS for ART detection at 12 months (64). At 12 months we will also collect blood for viral load through venipuncture, for those with no viral load result in the past 30 days.

14. Sample Size

Power calculation and sample size. A sample size of 290 participants will provide 85% power to detect an absolute difference of 20% or more in achieving viral suppression (e.g. 45% in the EUC arm vs. 65% in the intervention arm) at 12-months follow-up. This is based on a two-sided Fisher's exact test with $\alpha = 0.05$ and allowing for 20% attrition. Pilot data showed a larger difference between arms (50% in the EUC arm vs. 75% in the intervention arm), suggesting this should be a conservative sample size estimate. For the secondary outcomes, this sample size will allow detection of an effect size of 0.37 or greater on the continuous depression scale (based on $\alpha = 0.05$, a two-sided test of difference between two independent means and the same level of attrition). The sample size will also provide 90% power to detect a 20% difference in the proportion with ≥90% adherence as was seen in our pilot data (also Fisher's exact test, $\alpha=0.05$ and 20% attrition). This is based on our pilot data, national data (65) and other research (8, 35).

15. Recruitment Procedures.

Participants will be recruited by research assistants at the ART clinics at Marondera Hospital initially, and at Chitungwiza Central hospital. We will recruit from all patients identified as having a detectable viral load in the past 2 months, and from those at high risk of viral non-suppression (e.g. PLWH with missed appointments, those who have 'defaulted' medication, or those who self-report adherence problems). Potential participants will complete a brief study screener to assess for likely depression (see section 13, Participant Timeline). If they meet inclusion criteria, study recruiters will invite participants to complete the informed consent process and complete the baseline assessment. In those who screen positive for depression and are at high risk of viral non-suppression but have not had this confirmed by blood test in the last 2 months, baseline assessment will include a viral load test to ensure eligibility (see Baseline study visit***).*** We will recruit from individuals initiated on ART for at least 6 months, which will allow for viral suppression to have been achieved if the person has been adherent to medication they are not resistant to, and to allow for the person to have gained some experience with the challenges of ART adherence.

Consent Procedures. Informed consent procedures will occur before study enrollment. A Participants who have met preliminary inclusion criteria assessed by the brief study screener and are interested in participating in the study will be invited to complete the informed consent process. A consent form will be signed by each participant following a comprehensive and interactive explanation by staff. Study personnel will receive training regarding procedures required to obtain informed consent, and training will be completed yearly in order to continually reinforce such procedures. This Good Clinical Practice training is provided face to face by designated trainers from the Medical and Research Council of Zimbabwe. All study personnel will also be appropriately trained in the ethical conduct of human subjects research and required to re-certify every two years. The consent form will include all of the 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 they can withdraw from the study at any time, and that study participation is in no way related to their care received at the clinic.

Participants will be asked to consent to study procedures, consent to release of information from their medical record regarding HIV disease status and treatment, and consent to share results of study assessments with their treatment team. All participant questions will be answered before they are asked to sign the consent form. If there is any indication that the patient is unable to fully understand and/or retain the information provided, but is indicating consent, their capacity to provide consent will be assessed by the Site PI, a psychiatrist. The Site PI (or designee, in the event of absence) will review all informed consents within one week of their completion.

All procedures and protocols will be approved by the coordinating site KCL Research Ethics Committee, the MGH IRB, and the University of Zimbabwe Medical Research Council of Zimbabwe IRB and also the National Research Council of Zimbabwe IRB before study initiation.

Consent for study assessment results to be shared with treatment team. Those who consent for the information from their psychological assessments including the results of the mental health diagnostic assessment (MINI) will have a letter sent to their treatment provider/team. This letter will document the mental health conditions for which the participant meets diagnostic criteria. The letter will also inform the participant's treatment team that participants who are receiving concomitant psychopharmacological treatment for mood disorders continue to be eligible to participate in the study.

Section 3b: Methods - assignment of interventions

16. Allocation

16a Sequence Generation
Consideration was given to stratify based upon current antidepressant use or alcohol or substance use disorders. However, it is expected that less than 4% of the sample will be prescribed antidepressants, and the documentation of alcohol or substance use disorders as influencing psychosocial treatment effects in Zimbabwe is absent from the research record. As programming of REDCap randomization must take place prior to any data collection, a second randomization table will be programmed into REDCap to allow for stratification by recruitment site, in the event that a second recruitment site is needed. This second randomization table will not be used unless a second recruitment site is needed and amendments to the protocol which would allow for the use of a second recruitment site are approved by the ethics committee.

Eligible participants will be randomly assigned to receive either the stepped care-AD intervention or EUC.

16b. Allocation Concealment Mechanism Participants will be randomly assigned in a 1:1 ratio using a block randomization procedure coordinated through REDCap. The randomization tables that power the REDCap randomization module will be created using SealedEnvelope.com. Only the data manager will be able to upload the randomization tables to REDCap and administrator credentials from a Massachusetts General Information Systems Manager are required to download the randomization tables once data collection has begun.

16c. Research assistants will enroll participants and the University of Zimbabwe Project Manager will use REDCap to randomize participants

17a. Blinding (Masking) clinician-administered measures (PHQ-9, EQ-5D-3L, self report adherence) at follow up, will be delivered by an independent assessor, who will be hired at the start of participant recruitment and is blind to study condition. The independent assessor will be trained to conduct the clinician-administered assessments by the local Clinical Psychologist. At the beginning of the follow-up visits, the independent assessor will introduce themselves and their role to the participant, emphasizing their need to be blinded to study condition. If the independent assessor becomes unblinded during the course of a visit, a study staff member who is blinded to the participant's randomization condition will listen to the session audio recording to ensure that the assessments were conducted in an un-biased manner. Future visits will be conducted by a different independent assessor, blind to study condition.

17b. Safety information for this study will be reported to the Data Safety and Monitoring Committee in a manner stipulated by the committee. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the Committee as no statistical comparisons will be made between Stepped Care-AD and EUC until the end of the trial. Unblinded data will not be released to the investigators unless necessary for safety reasons.

Section 3c: Methods - data collection, management, and analysis

18a. Data Collection Methods

Primary outcome

1. Blood (plasma) will be collected for all randomized participants at 12 months follow up. Viral suppression, defined as <1000 copies/mL (dichotomous outcome), at 12-months post-randomization. This measure will be taken from the medical record if there is viral load measure recorded within 30 days of the expected visit date or through study specific assay if not in the medical record.

Secondary outcomes

1. Depression at 12 months post randomization measured as the total score on the locally validated Patient Health Questionnaire (PHQ-9). It derives its scoring system from the DSM-IV criteria for depressive disorders. Each of the nine items is scored from 0 (not at all) to 3 (nearly every day). It is used as a continuous score ranging from 0 (no depressive symptoms) to 27 (all symptoms occurring daily/nearly daily).

2. Adherence to ART medication at 4, 8, and 12-months post randomization assessed as the proportion of the sample achieving at least 90% adherence in the past month assessed through pharmacy refill.

3. Self-reported adherence to ART medication at 4, 8, and 12-months post randomization assessed as the frequency of adherence in the past 30 days measured usinga score derived from a three item questionnaire adapted from Wilson et al., (2015) (66).

4. HIV viral copies/mL at 12 months post randomization follow up will be extracted from the patient medical record or by study specific assay if the information is not available in the medical record.

Tertiary Outcome measures

Cost Effectiveness Assessment

The cost effectiveness of the task-shifted stepped care-AD intervention on viral suppression and quality of life at 12-months. These will be measured as detailed below

Client Services Receipt Inventory – In order to calculate the total costs of the health care services used by each study participant, we will collect service use information from hospital records and from participant self-report at baseline, 4-, 8-, and 12-month follow-up. The use of services will be collected using an adapted version of the Client Services Receipt Inventory that will be developed and piloted using the set-up phase of the study and based on work undertaken in similar settings (67).
Therapist Records – Detailed information on the use of stepped care-AD and EUC will be collected from therapist records
EQ-5D-3L – Based on the Shona dialect of the research site, a quality of life measure, will be collected at baseline and follow-up assessments. Quality-adjusted life years will be calculated using country-specific health states (68).

Exploratory outcome measures

1. Exploratory mediators of treatment effects on depression and adherence will be explored using a locally-developed social support measure (59), Adherence Self-Efficacy Scale, (a questionnaire that measures confidence in being able to take HIV medication as prescribed), and The Problem Solving Skills subscale of the Problem Solving Inventory (a questionnaire which assesses use of adaptive problem solving skills, previously used in the region) (69).
2. Exploratory mediators of treatment effects on viral suppression will explored using PHQ-9 for depression and a composite measure of adherence (self-report, pharmacy refill, and DBS measures of adherence will be used as indicators of an adherence latent variable in line with established procedures
3. Sex, depression severity and household assets, will be tested as moderators of the treatment effect on viral suppression, adherence, and depression. (Note: demographics will be summarised in the main trial paper, but will also be looked at further in exploratory analyses outside of the main paper).

Other Exploratory measures

Most measures described below are taken to facilitate study processes or are to be studied outside the main trial.

1. Participants will complete the PHQ-9 at baseline. The 9 item measure can be used as a binary measure, with a cut-point of =>10 recommended in the US (sensitivity and specificity for major depression of 88%) (70). In Zimbabwe, a cut of point of >=10 provided sensitivity 91.28% and specificity of 50.43% with 73.48% correctly classified. The PHQ-9 includes an item on suicidality. Those deemed to be at more than minimal suicidal risk will undergo comprehensive assessment for suicidal risk (see section on Protection of Human Subjects for more detail).

2. Medications (ARV and Antidepressants): During baseline assessment, patients will provide information regarding all their medications (psychiatric, and HIV). When completing assessments at every study visit thereafter, patients will be asked to report any changes to their medication regimen. These changes will be recorded and cross checked with clinic chart review. Any initiation or changes to antidepressant medications will be tracked across all participants.
3. AUDIT– We will screen for alcohol use with the Shona version of the AUDIT which is a screen for alcohol use disorders. It uses questions about frequency and amount of alcohol (71).
4. The PCL-5 and LEC-5, a locally validated post-traumatic stress disorder (PTSD) checklist will be used at baseline, 4, 8 and 12 month follow ups.
5. Mini International Neuropsychiatry Instrument (MINI) – The MINI will be used to assess depression at baseline. This short structured diagnostic interview for the DSM-IV is one of the most widely used instruments to reliably determine Axis I psychiatric disorders in clinical populations (72-74). It is designed to be used by either clinicians or trained lay individuals. The MINI will also be used to characterize the sample with respect to dysthymia. The US-based investigators have extensive experience using the MINI in clinical trials and will conduct weekly supervision meetings over a video-calling service to ensure assessment reliability.
6. Demographics – This questionnaire includes items regarding age, sex, income generating activities, current or recent pregnancy and educational history.
7. Mode of HIV infection – This is a single item question assessing risk factors for likelihood of means of HIV infection asked only at baseline.
8. Depression treatment and non-study therapy – At every visit, participants will be asked if they have had any changes to their medication or other current treatment for depression.
9. CD4 from Medical Record - Absolute CD4 cell number will be extracted from participants' medical record at baseline and at 12 month follow up (75).
10. Psychosis Screener - will be used at baseline only to assess exclusion criteria
11. Viral Load - At baseline, as part of the inclusion criteria, this will be measured as part of the national testing program, or by research screening of high-risk participants who do not have a recent VL result (e.g. missed appointments, defaulted medication, as described above). Testing will be carried out by the Viral Load machine at the recruitment clinic where possible, or by study specific testing using standardised platforms with plasma or DBS. At 12 month follow up testing will be carried out using standardized platforms with plasma and will be reported as the proportion of patients achieving a viral load <1000 copies/mL.
12. DUDIT - We will screen for alcohol use with the Shona version of the DUDIT which is a screen for substance use disorders (76).
13. BARTA - participants will complete the Barriers to AntiReTroviral Adherence for people living with HIV in Zimbabwe (BARTA). A 20-item measure assessing barriers to ART adherence for adults living with HIV in Zimbabwe. The measure is scored on a 5-point Likert scale from 0 – never to 4 – always (77).
14. HIV Related Dementia Scale - will be used at baseline only
15. Hospital Anxiety and Depression Scale (HADS) anxiety sub-scale – will be used at baseline, 4, 8 and 12 month follow up to measure anxiety (78).

Characterizing the adherence behavior of PLHIV who do not meet eligibility criteria for depression

Participants who complete the brief screening assessment and are identified at high risk of viral non-suppression (due to having had a detectable viral load (>1000 copies/mL) in the past 12

months, or reporting missed appointments or non-adherence to ART), but do not score above 2 on the PHQ-2 and are not eligible for full trial baseline assessment will be invited to complete a short questionnaire. This will include the Barriers to AntiReTroviral Adherence for people living with HIV in Zimbabwe (BARTA) (77) and a 3 item self-report adherence measure (66). We will also capture their age, gender and recent vial load. This will allow for characterization of the behavior of those who have a high viral load, or are at high risk of viral non-suppression, but are not depressed.

Participants will receive a thorough explanation of the purpose and procedures of these measures through informed consent procedures delivered by the trained research assistants. Participants will have the opportunity to ask questions. The consent process will include consent to study procedures and consent to release of information from their medical record regarding HIV treatment.

All data will be recorded in RedCap and follow the same data storage procedures as the full trial data (refer to section 19).

Research Domain Criteria

The complexity of most evidence-based treatments for depression is one barrier to making them accessible to people living with HIV in the community in low and middle-income countries (LMICs). Another barrier is lack of knowledge as to who will benefit most. In low-resource settings is critical to rationalize implementation of interventions in line with evidence. The heterogeneity of depression symptoms, especially in LMIC contexts, and co-morbidities with other common mental disorders, means that we urgently need tools to guide the implementation of cost-effective depression care. There is strong scientific premise that disruptions in brain systems of cognitive control and negative valence contribute to depression and may predict depression treatment response. We therefore aim to use several tests that measure brain disruptions to assess the role of cognitive control and negative valence in determining response to treatment for depression, in PLWH in Zimbabwe.

Aims:

1. To determine baseline associations between cognitive control, negative valence, and standard measures of depression in PLWH. Hypothesis: Self-report and performance on measures of cognitive control and negative valence will be significantly associated with depressive symptomatology (PHQ-9, observer-rated Mini International Psychiatric Interview). This will be done by integrating RDoC measures into the baseline assessment of the parent clinical trial in 100 PLWH.

2. To determine if cognitive control and negative valence predict depression treatment response in PLWH. Hypothesis: Self-report and performance on measures of cognitive control and negative valence will significantly predict depression treatment response (PHQ-9 change). This will be done by using the data collected in Aim 2 and using depression outcome data from the parent trial.

Our proposed research has considerable potential to increase knowledge about who most benefits from different levels of scalable stepped care neuro-health interventions in PLWH in a LMIC context, and thus herald a new era of implementation science.

Behavioral measure: Parametric Go/No-go/Stop Task (PGNGS) is a 10-minute computerized task measuring sustained attention, inhibitory control, and processing speed. The task has three

levels presented in ascending difficulty, presented at a rate of 500ms per symbol where participants will be asked to press certain keys depending on certain letters appearing on the screen.

Self-Report Measure: The Short Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (S-UPPS-P) **.** The UPPS-P model of impulsivity assesses behavioural inhibition through dimensions of negative urgency, premeditation, lack of perseverance and sensation seeking, through 20 items using a four point Likert-type scale. We have translated the items into Shona, and will be using the S-UPPS-P to assess self-reported cognitive control.

Self-Report Measure: Webexec**.** The Webexec is a short self-report measure of problems with executive function, originally designed for use in Internet-mediated research (E.g. online surveys). It consists of six items that assess attention, planning, and inhibition. We have translated the items into Shona, and will be using the Webesec to assess self-reported cognitive control.

Facial Emotion Perception Test (FEPT) is a 10-minute computerized task that assesses the ability to categorize facial expressions. The FEPT involves briefly showing participants pictures of faces with one of four target emotions (fear, anger, happiness, sadness) or a neutral expression

Assessing the Interrelationships between COVID-19-Specific Distress and trial outcomes and COVID-19 outcomes

Though there is a dearth of research on the connection between HIV and COVID-19 acquisition, PLWH may experience comorbidities such as cardiovascular disease and chronic lung disease, that may place individuals at greater risk for severe COVID-19 symptoms (79-81). Additionally, individuals with psychiatric conditions, such as anxiety and depression, may find engaging in COVID-19 treatment more challenging and that treatment is less effective (82). PLWH and comorbid depression also have poorer engagement in HIV care, which could lead to increased susceptibility to opportunistic infections and, in turn, to increased risk of SARS-CoV-2 acquisition (35, 83).

Identifying patterns of COVID-19 risk among PLWH is of utmost importance in Zimbabwe, where HIV prevalence rates border of 15%7. While not yet reaching the level of widespread community transmission seen in Europe, Asia, and the United States, COVID-19 rates in Africa are steadily increasing. As the scope of the pandemic widens in Sub-Saharan Africa, it is critical to assess how populations who face severe health disparities, such as PLWH and mental health comorbidities, are impacted by the virus.

Participants enrolled in the TENDAI trial will be asked to complete COVID-19-specific self-report at their regularly scheduled study visits to estimate and quantify COVID-19 specific distress (COVID-19 specific health anxiety, health anxiety, intolerance of uncertainty, anxiety sensitivity) and to relate these measures of distress to trial study outcomes.

COVID-19 specific measures: COVID-19-specific intolerance to uncertainty104, COVID-19 symptom checklist and anxiety, COVID-19 risk appraisal, and level of medical care received after COVID-19 diagnosis. Additionally, when available, assay of COVID-19 antibodies will be performed from DBS.

Understanding the priorities, enablers and barriers of implementing the TENDAI intervention (PST-AD) for people living with HIV and depression in Zimbabwe

Qualitative methods informed by implementation science frameworks will be used to understand participant experience of receiving the intervention, and enablers and barriers of implementing the TENDAI intervention.

The aim of this sub-study is to a) explore participant's response to the intervention and b) gather evidence to inform a future implementation study of the TENDAI intervention. This will be achived by identifying relevant implementation science frameworks and using qualitative methods to understand the context of implementation, implementation priortieties, and barriers and facilitators, to inform an implementation strategy.

Aproximately 45 participants will be recruited. This will be 30 adults who have received the intervention, 4 interventionists and 11 health care providers and policy makers. All participants will complete informed consent procedures. The topic guide(s) have been informed by key implementation science frameworks. Participants who have received the TENDAI intervention will be invited to take part in the exit interviews at 4 or 8 month post randomization follow up. The first half of the interviews with participants who have received the TENDAI intervention will focus on understanding patient's experience of receiving the intervention and response to the intervention. The second half will focus on understanding the context of implementation including individual level barriers and facilitators. Interviews with health care workers, policy makers and interventionists will focus on understanding the context of implementation including barriers and facilitators.

Interviews will be audio recorded and will be translated and transcribed for analysis.

Understanding the experiences, views and acceptability of antidepressants to help with symptoms of depression for people in TENDAI intervention (PST-AD) in Zimbabwe.

Qualitative methods will also be used to explore beliefs about antidepressant medication. Understanding the acceptability of antidepressants will be valuable to inform an implementation strategy of the TENDAI stepped care intervention. This is because, for participants whose depression does not achieve remission 6 weeks after starting the TENDAI PST sessions (see section 11a Interventions 'Step 2') a psychopharmacological assessment may result in the prescription of an antidepressant.

In Zimbabwe, psychological interventions based on problem-solving therapy have demonstrated effectiveness as first-line treatments for depression (94,14). However, approximately 50% of treated individuals do not respond to these therapies. To ensure the provision of high-quality mental health care, it is essential to establish sustainable and effective alternative and stepped treatment options.

Globally, antidepressants, especially Selective Serotonin Reuptake Inhibitors (SSRIs) like fluoxetine, are widely prescribed for people with depression in primary health care settings. These treatments are cost-effective, safe (95) and also recommended for use in low-income countries by the World Health Organization's Mental Health Gap intervention guide (96). However, in Zimbabwe access to these medications has, until recently, been very limited (97).

Thus, a significant gap in understanding their acceptability, feasibility, and effectiveness has emerged.

We aim to recruit approximately 10 trial participants with depression and invite them to an in-depth interview. We will recruit participants who did not respond to psychotherapy or who still reported depression symptoms such as sadness or thinking too much during their follow up study visit, including those for whom an antidepressant was prescribed. The interview topic guides will be informed by the Theoretical Framework of Acceptability, Health Equity Framework, and the Necessity-Concerns Framework, to ascertain participants' personal beliefs about taking medication for depression. For those who were offered and accepted Fluoxetine, we will explore their experiences of taking the medication.

Furthermore, a workshop using human centred design with 20 mental health specialists will be used to develop a prototype implementation strategy for prescribing Fluoxetine in primary healthcare settings in Zimbabwe. Human Centred design is an approach to problem solving that uses participatory methods to define the challenge, brainstorm ideas to address the challenge, and test the intervention design. The workshop will be used to help address barriers faced by nurses in initiating, monitoring and supporting people who may benefit from medicines that improve depression.

Interviews will be audio recorded and will be translated and transcribed for analysis.

List of proposed measures. See Appendix 1 for data collection forms.

Measure	Baseline	Intervention Sessions	4mfu	8mfu	12mfu
MINI	X				
PHQ-9	X	X (Sessions 3, 4, 5, 6)	X	X	X
PCL-5 and LEC-5	X		X	X	X
Medications (ARV, Antidepressant)	X		X	X	X
AUDIT	X		X	X	X
Viral Load	X				X
CD4 from Medical Record	X				X
Blood (plasma) for viral load					X
DBS for ART detection	X		X	X	X
Psychosis screener	X				
Self Report Adherence Questionnaire	X		X	X	X
Pharmacy Refill Data	X		X	X	X

Demographics	X				
Mode of HIV infection	X				
Depression treatment and non-study therapy	X	X	X	X	X
Client Services Receipt Inventory	X		X	X	X
Therapist Session Records			X		
DUDIT	X		X	X	X
EQ-5D-3L	X		X	X	X
Social Support	X		X	X	X
HADS anxiety subscale	X		X	X	X
Adherence Self-Efficacy	X		X	X	X
BARTA	X		X	X	X
Problem Solving Inventory (Problem Solving Skills subscale)	X		X	X	X
HIV Related Dementia Scale	X				
PGNS	X				
BRIEF-A	X				
I-FEPT	X				
COVID-19 Distress	X	X	X	X	X

Integrity of diagnostic assessment. All baseline diagnostic assessments will be conducted by criterion-trained study personnel and all clinician administered out-come measures (PHQ-9, EQ-5D-3L and self report adherence) at follow-up assessments will be conducted by an assessor blind to study condition. Training will include review of videotapes and participation in live diagnostic interviews. The certification procedure requires the adherence counsellor to (1) view recorded and live administrations by senior interviewers and the comparison of the trainees' ratings to that of the senior interviewer, and (2) administer interviews in the presence of the senior interviewer with the requirement of the trainees' until adequate diagnostic matching.

Independent assessors. The PHQ-9, EQ-5D-3L and self report adherence at follow-up visits (4, 8, 12-months) will be administered by a trained independent assessors (IA) in order to minimize bias. The IA will specifically instruct participants at each follow-up assessment not to disclose their condition assignment to the assessor.

Reliability of diagnostic and efficacy ratings. Inter-rater agreement will be assessed via evaluation of audiotapes of baseline pre-randomization diagnostic interviews which includes the PhQ-9. Inter-rater reliability (kappa) will be calculated for each of the diagnostic categories. A minimum of 15 Independent Assessor audio recordings from the first follow-up visit will be scored on competency by a study clinician who was not involved in the visit, and measures of

concordance (e.g., intra-class correlation coefficient for continuous measures and kappa for dichotomous measures) will be calculated. Discrepancies in scoring will prompt discussion and recalibration of clinician administered assessment procedures as necessary. To prevent observer drift, periodic recalibration of raters will be carried out using reliability assessment data.

Therapy training. The therapy manual developed and adapted in the R21 by the current study team will be used. The local Clinical Psychologist will be the primary supervisor of the adherence counsellors, and will be supervised by Dr. Mangezi (the site PI) Dr. O'Cleirigh and the research psychologist (MGH) will support Dr. Mangezi and the local clinical psychologist, through weekly phone calls and video calls and at least twice annual site visits to provide in-person training the study adherence counsellors, who conduct the intervention, and their supervisors.

Therapy supervision. Supervision of study therapists will take place on a weekly basis. The Zimbabwe Programme Manager has primary responsibility for ensuring weekly supervision of the adherence counsellors.

Assessment of intervention integrity. The therapy adherence measure will assess the extent to which therapy activities were implemented in a manner that is maximally consistent with the intent of the therapy manual. All treatment sessions will be recorded and a random selection of 10% of sessions for each therapist will be translated (orally) and rated by the clinical psychologist and the Zimbabwe Programme Manager.

18b. Participant retention. The research assistants will track participant retention, which will be reviewed weekly by the on-site Zimbabwe Programme Manager and discussed in weekly PI/ video conferenced team meetings. Procedures to maximize retention include reimbursing participants for their time (the visits they attend) and sending text message reminders the day before their scheduled appointments. We will also collect extensive locator information (e.g., contact information of two significant others with whom the participant is in regular contact; involvement with HIV organizations). We will make efforts to retain individuals who move to a non-study site for their HIV care and are willing to complete follow-up. The study team will endeavor to obtain at least primary and main secondary (depression measured by PHQ-9 and adherence measured by self report and pharmacy refill) on all participants regardless of their attendance at intervention/clinic visits unless they ask to be withdrawn from follow-up data collection. The study team will call participants to invite them to return to clinic to obtain this data. Where participants are unable to travel to the clinic to complete follow up assessments (for example if participants cannot travel to the clinic because of C-19 lockdown travel restriction), participants will be invited to complete assessments over the phone with a trained assessor. Where participants are unable to travel to the clinic to attend intervention sessions, sessions 4, 5 and 6 may be conducted by telephone. Where participants can not be reached by phone a home visit may be conducted. Consent for telephone calls and home visits will be sought at baseline.

Attrition safeguards/protection of loss of data. A notable methodological consideration pertaining to the proposed research is protection against attrition. Our research groups in Zimbabwe, London and Boston have conducted numerous clinical intervention studies. In our previous work we have learned that individuals are best retained in studies when (1) financial remuneration is offered, (2) there is familiarity with study personnel with this population (e.g., ability to effectively establish rapport), (3) there team-based persistence in conducting follow-up assessments, and (4) intervention sessions happen at the HIV care facilities. We have outlined

our approach to retain maximum number of participants in the proposal. However, it is worth noting a number of key issues we thoughtfully considered to lessen attrition. In clinical research studies, attrition overall occurs from three major sources: (a) mortality, (b) refusal to participate, and (c) loss of contact.

Mortality. Participant mortality is of particular significance in epidemiological studies of the aged and other groups who are medically "at risk." However, mortality does not pose a significant problem in this study due to the age and health status of our proposed sample. Although the study sample will be participants living with HIV, we do not anticipate attrition from mortality to be a significant concern.

Refusal to participate. Participants who are successfully recruited into the study but later refuse to participate in subsequent intervention sessions pose a threat to the proposed study. This could be particularly true if subjects with depression show higher refusal rates (attrition bias). Eaton and colleagues have examined whether psychopathology and anxiety disorders in particular are associated with increased refusal rates (84). They also found that after controlling for relevant demographic factors, subjects with a psychiatric disorder were no more likely to refuse participation than subjects without a psychiatric disorder (adjusted relative odds ratio of .93). Research Assistants will explain to participants the importance of attending all study visits and the value of their time when completing informed consent, and at each follow up visit. In addition, study participants will receive modest monetary compensation for the completing the last study assessment, thus reducing further the likelihood of subject refusals.

Loss of contact. A second source of attrition involves those subjects who are successfully recruited into the study but who cannot be located for later-stage intervention sessions or follow-up assessments. Like attrition due to subject refusal, attrition due to loss of contact poses a threat to the proposed study. We will employ several strategies to minimize this source of subject attrition. These include: (a) obtaining the name of a person who will typically know the subject's whereabouts (e.g., mother, partner), and the names of at least two other individuals that the subject consents to allow us to contact should contact be lost and (b) periodic phone calls and texts (if feasible) to subjects to keep them informed of project follow-up. These are realistic procedures as mobile phone possession and use are widespread within the Mashonaland East Province where study recruitment will take place.

Participant adherence and incentives for participation. To minimize attrition, we will use multiple strategies to reduce drop-out. Potential participants will be invited to participate in the baseline assessment within one week of completing the screening. During the baseline assessment, participants will receive a thorough explanation of the study treatments, requirements, and follow-up procedures and why their continued involvement is important. Study staff will emphasize the patient's responsibility as a research participant, reiterate confidentiality, work to develop good rapport, and be trained on uniform procedures concerning late or missed appointments. Participants will be asked to provide contact information for two alternate people they would feel comfortable having us contact in an effort to reach them. This may include an address of a relative or friend where participants may have no reliable fixed address. We expect that a small number of participants may not complete the full baseline assessment. Participants not completing baseline will not be randomized and will therefore not be included in follow-up assessments. We will make a concerted and systematic effort to facilitate attendance to all treatment sessions. This task will be accomplished by: (1) scheduling sessions at a time that is convenient for each participant; and (2) sending reminder text messages before each session. Staff will be trained to send an SMS message to remind participants of their scheduled appointments three days and 24 hours prior to each scheduled

follow-up session. This approach has been used successfully in past work, and in the past, we have achieved an 84% retention rate at 3-month follow-up (85). 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. Additionally, reimbursement will be given in line with local standards for a providing a brief amount of data at clinical sessions, as discussed above.

19. Data management

Data management organizational structure. The REDCap database will undergo a systematic and rigorous editing process prior to the start of data collection. The research assistants will be assigned monthly data checks (20% of the trial data collected) by the data manager or University of Zimbabwe Project Manager and discuss any problems and questions with the study staff and the investigator team at the subsequent team meeting. Data management formal reports on completed data checks will be pulled monthly. These reports of data records will be evaluated once a month during the final team meeting of the month. To help ensure data protection, backup copies of the full data record, generated via REDCap report and uploaded to a secure server at MGH weekly, will be available. Additionally, our hard copy record systems, where the assessment is completed on paper due to a failure of electronic tablets, will be maintained in fire-resistant locked cabinets at each site.

Data collection occurs at the Marondera Provincial Hospital and, potentially later, Chitungwiza Central Hospital study implementation sites. Data from study assessments and questionnaires will be collected on study tablets using the REDCap Mobile App. Data entered into the app will by synced daily with the REDCap project stored behind the MGH firewall. In addition, data on adherence counsellor training, independent assessor training, clinical supervision, participant progress through the study procedures will also be entered and uploaded. This project management data will be entered as close to real time as possible to facilitate data management and monitoring of study operations. The Data Manager at the MGH site will provide regular reports regarding recruitment initiatives and participant progress in the study to Dr. O'Cleirigh and these reports will be summarized at the Project Management Committee Meetings. These procedures are further specified in the Data Safety and Monitoring section (section 21). Confidentiality is assured as participants will be referred to by participant ID number, visit number, and date of visit in REDCap and during supervision. By recording the study data in this manner, the information can be considered 'pseudo-anonymised', and therefore, compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 ("HIPAA"). Further information on Data Management Procedures will be found in the TENDAI Trial Data Management Plan.

Data Validation
Each month, a random subset of visits from the previous month (20%, or the closest whole number) will be assessed for data quality and accuracy (missing data, discrepancies in responses between questionnaires, data that is out of range). These checks will be documented using the Data Review and Correction form in the Project Management Database on REDCap. Quality assurance checks will be assigned to Research Assistants by the Data Manager or the University of Zimbabwe Project Director. The Data Manager will ensure that the staff member conducting the check was not involved in the collection of data for that visit. Quality assurance checks will be completed within 2 weeks of assignment. Higher order data checking will be done by the statisticians (e.g. data completeness checks and higher-level logic checks, etc.). Further information on data validation will be found in the TENDAI Trial Data Validation Plan.

Centralized data repository (MGH Site). The study PI at Massachusetts General Hospital has coordinated research initiatives over the past 5 years that utilize centralized data management from multiple study sites and have established procedures and technologies in place. Dr. O'Cleirigh will oversee that aspect of the study and the MGH Data Manager will have the operational responsibility for data management as described previously. Specifically, the MGH team will develop a study specific data management protocol and standard operating procedures for the creation and testing of all study questionnaires, data collection, quality control, and data extraction. The MGH team will provide ongoing oversight of data management throughout the study, and will be responsible for generating reports and datasets for quality control and data analysis. The Data Management team will make data available to the study statisticians for data checking and final analysis. Data management reports will be made to the DSMBby the MGH team.

REDCap. All data management activities will utilize REDCap, a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. REDCap provides secure, HIPAA compliant, web-based applications 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.

20a. Statistical methods

Preliminary Analyses. Variables will be summarized using appropriate summary statistics. In the preliminary analyses, we will also examine the equivalence of the random assignment of groups with regard to key baseline characteristics. This will involve non-statistical comparison of the treatment groups on sociodemographic characteristics, adherence-related variables, depression and biological markers (e.g., viral load).

Primary and Secondary Outcome Analysis. Effectiveness results will be reported following CONSORT guidelines (86) by intention to treat analysis and a-priori defined variables. These analyses will be conducted in Stata version 15 or IBM SPSS. For most analyses we will use generalized linear models (GLM) with properly-chosen (based on the distribution of dependent variable) link functions to analyze longitudinal data for each major study aim. The GLMs will be either be mixed effects models (e.g. for continuous PHQ-9 depression measure) or estimated using generalized estimating equations with robust standard error estimates (GEE e.g. for categorical viral load) to account for repeated measures of the outcomes. Time by treatment interaction effects will be included in models to allow the effects to differ at different time points. All tests will determine significance at alpha =0.05.

Primary Aim. It is hypothesized that the intervention will be associated with a significant increase in the proportion of those achieving viral suppression (primary outcome) compared to the EUC condition at 12 month follow up. Viral suppression is defined as viral load < 1000 copies/ml.

Secondary Aims. It is hypothesized that the intervention will be associated with significant reductions in depression (secondary outcome) and significant increases in the

proportion of the sample achieving 90% adherence compared to the EUC condition. For the depression outcome (assessed by independent assessor blind to randomization condition, using PHQ-9 continuous score), we will assess the difference in means between the stepped care-AD intervention and the EUC condition. For the adherence outcomes, we will compare the difference in proportion of those randomized to each condition meeting >90% adherence (assessed via pharmacy refill), and for self-reported adherence to ART medication at 4, 8, and 12-months post randomization (assessed as the frequency of adherence in the past 30 days).

Secondary outcomes measures

1. Depression at 12 months post randomization measured as the total score on the Patient Health Questionnaire (PHQ-9).
2. Adherence to ART medication at 4, 8, and 12-months post randomization assessed as the proportion of the sample achieving at least 90% adherence in the past month assessed through pharmacy refill.
3. Self-reported adherence to ART medication at 4, 8, and 12-months post randomization assessed as the frequency of adherence in the past 30 days.
4. HIV viral copies/mL at 12-months post-randomization follow-up.

Tertiary outcomes measures

1. The cost effectiveness of the task-shifted stepped care-AD intervention on viral suppression and quality of life at 12-months.

Exploratory outcome measures

1. Exploratory mediators of treatment effects on depression and adherence will be explored using a locally-developed social support measure, Adherence Self-Efficacy Scale, and Social Problem Solving Self-Efficacy and Skills.
2. Exploratory mediators of treatment effects on viral suppression will explored using PHQ-9 for depression and each of self-report, pharmacy refill, and DBS measures of adherence as potential mediators, then also a composite measure of adherence using all three will be used as indicators of an adherence latent variable in line with established procedures (60)
3. Sex, depression severity and household assets, will be tested as moderators of the treatment effect on viral suppression, adherence, and depression.

20b Methods for Additional Analyses

Specific Aim 2a: Mediation. Exploratory mediators of treatment effects on depression and adherence will be explored using a locally-developed social support measure, Adherence Self-Efficacy Scale, and Social Problem Solving Self-Efficacy and Skills. If results indicate that the intervention significantly increases the proportion of viral suppression as compared to EUC, we will assess the extent to which this effect operates through the potential mediating effects of depression or adherence. Exploratory mediators of treatment effects on viral suppression will explored using PHQ-9 for depression and each of self-report, pharmacy refill, and DBS measures of adherence as potential mediators, then also a composite measure of adherence using all three *indicators* of an *adherence latent variable* in line with established procedures (60). We will also propose to study mediation where there is no treatment effect to gain information about why the treatment wasn't successful. Structural equation modelling will be used for these analyses, using MPlus software (60). We will initially propose to explore the

mediators in simple mediation models (87), where we use an earlier measure of the mediator and the 12-month measure of the outcome to respect the temporal ordering implied by mediation hypotheses. For promising mediators, we will explore longitudinal models incorporating repeated measures of the mediator and outcome, allowing us to better account for potential sources of bias such as measurement error, and to gain a more in-depth understanding of the mediating processes (54, 87).

Specific Aim 2b: Moderation. An exploratory moderator analysis will be undertaken to help clarify for whom and under what circumstances the intervention works using a-priori defined modifiers (sex and depression severity at baseline measured using PHQ-9). These will be assessed in models using intervention group by moderator interaction arms.

Specific Aim 3: Cost Effectiveness. Cost-effectiveness results will be reported following CHEERS guidelines (88). The aim of the economic evaluation, led by senior economist Dr. Barrett, is to provide information for local decision makers, government and international donors. The total cost of the intervention, drug use plus all services used, will be calculated by combining service use with a unit cost. For each service use item collected in the CSRI, a unit costs will be collected identified. The work to collect unit costs will be undertaken over the course of the study by the dedicated health economist, using local information, such as health service accounts, wherever possible. Alternative unit costs sources such as the WHO-CHOICE resource will also be used if necessary. First, the mean average total cost in each randomized group will be calculated and compared between the two groups using standard t-tests, despite the likely skewed nature of the data because of a preference for reported means in costs (89). As is common in the analysis of cost data, the robustness of the mean cost comparisons will be confirmed through the calculation of nonparametric bootstrapped confidence intervals (90). The primary cost-effectiveness will consider costs together with the dichotomous primary outcome measure (viral suppression <1000 copies/mL), generating information on the cost per successful case and the probability that the PST-AD is cost-effective compared to enhanced usual care given available information. A secondary cost-utility analysis will also be completed, which will report the cost per QALY of stepped care-AD intervention compared to enhanced usual care. Analyses will be adjusted for costs and outcomes. Sensitivity analyses will be carried out to test the robustness of costing assumptions to variation. Conclusions and recommendations will be made for different stakeholders.

20c Missing Data. We will also assess missing data patterns. The primary anticipated reason for missing data is attrition due to loss to follow-up. Based on our preliminary studies, we are accounting for as large as 20% attrition from randomization to the 12-month assessment (though we expect considerably less). The baseline characteristics of those that do not provide outcome data will be examined using logistic regression models with whether or not individuals provided outcome data as the dependent variable and baseline characteristics as independent/predictor variables. Any baseline variables that predict missing data will be included in final models to increase the plausibility of the missing at random assumption. Any missing baseline data itself will be imputed using simple imputation techniques (91). Multiple imputation is often not needed/recommended in trials (92), however, we will explore the need for multiple imputation of missing data, for example where adherence predicts missing outcome data.

Section 3d: Methods - monitoring

21. Data Safety and Monitoring Plan

21a. Data Monitoring: 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. The study will have a data safety and monitoring board (DSMB). A DAMOCLES DSMB charter outlining roles, meeting schedules and so on will be drafted in collaboration with the DSMB members and signed off by these members. A copy of the charter will be stored in the trial master file.

Membership of the DSMB. To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB 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 independent of the sponsor and will consist of members with experience in conducting clinical intervention research for psychiatric disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues.

The DSMB will be comprised of nominees from the Zimbabwe, London and Boston study sites, plus an HIV specialist from South Africa. The Committee will be chaired by Professor Rashida Ferrand who leads a research group conducting clinical and epidemiological studies on HIV infection in older children and adolescents and has been resident in Harare for more than 11 years; Dr James January, Head of the Dept of Community Medicine at the University of Zimbabwe; Professor Simon Gregson Director of the Manicaland HIV/STD Prevention Project in Zimbabwe, also a Zimbabwe resident; and Dr John Bradley Assistant Professor of Medical Statistics and Epidemiology at London School of Hygiene and Tropical Medicine.

Functional organization of the DSMB. The DSMB will meet annually in real time (most-likely by Zoom) and will be updated semi-annually with a report. The yearly meeting will be in the form of a conference call to review randomization, and adverse event data, as well as other data such as treatment retention rates determined in concert with the study statisticians. The adverse events will also be tracked and reported to relevant IRB committees.

21b. Study stopping rules. There are no formal interim analyses planned. If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the Committee shall have the discretion and responsibility to recommend that the study be terminated. However, the study does not have a pre-specified stopping rule.

22. Harms - monitoring of safety data by the DSMB. Safety information for this study will be reported to the Committee in an blinded or unblinded manner specified by the committee. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the Committee. Unblinded data will not be released to the investigators unless necessary for safety reasons. It is considered necessary for the purpose of monitoring the safety of the study that the committee review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between groups. This includes treatment retention rates and reasons for dropout.

Serious adverse events. Additional reporting to IRBs at Kings College London, Massachusetts General Hospital, MRCZ and JREC will be done within 72 hours of the SAE; reporting to NIH will be made according to their respective regulations governing SAE reporting. Expedited review by the DSMB will occur for all events meeting the Food and Drug Administration 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 DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will be required to be reported to the DSMB, 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. Notification by e-mail of all relevant reporting information shall be made to the DSMB Committee within 2 days of the occurrence of any SAE. Information will be reviewed by the DSMB and a determination made of whether there was any possible relevance to the study interventions.

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 summaries of the numbers of adverse events/of people with adverse events by treatment group. This data will be provided blinded or unblinded at the request of the DSMB. 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 Committee will also receive summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.

23. Audit - monitoring of data quality by the DSMB. Semi-annually, during the course of the study (starting after study start up), the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of participant intake and retention; summary reports describing participant compliance with visits, evaluations, and number of intervention sessions as described in the protocol; and a summary of the completeness and quality of key baseline variables needed to characterize participants, and their primary and secondary outcomes. The DSMB may request additional information from the study team if they deem it relevant to the monitoring of data quality and participant safety. The DSMB will meet annually, in person or via conference/video call, to discuss the report. At the end of the meeting, the DSMB will approve the report and provide the study team with recommendations for improving data quality and participant safety, if concerns are raised during the review of the report.

Section 4: Ethics and dissemination

24. Research Ethics Approval. All procedures and protocols will be approved by the coordinating site KCL Research Ethics Committee, the MGH IRB, and the University of Zimbabwe Medical Research Council of Zimbabwe IRB and also the National Research Council of Zimbabwe IRB before study initiation.

25. Protocol Amendments. Important protocol modifications will lead to amendment and a new version of the protocol, which will be reported to the above ethics committees.

26a. Recruitment and informed consent. Participants will be recruited from patients who are currently receiving HIV care from ART clinics at hospitals in the Mashonaland East Province, including Marondera Provincial Hospital and potentially Chitungwiza Central Hospital. Potential participants will be screened for eligibility and all individuals meeting inclusion criteria will be provided the opportunity to participate. A consent form will be signed by each participant

following a comprehensive and interactive explanation by staff. Study personnel will receive training regarding procedures required to obtain informed consent, and training will be completed yearly in order to continually reinforce such procedures. This Good Clinical Practice training is provided face to face by designated trainers from the Medical and Research Council of Zimbabwe. All study personnel will also be appropriately trained in the ethical conduct of human subjects research and required to re-certify bi-annually. GCP certificates will be provided to the KCL based Programme Manager and filed in the Trial Master File. The consent form will include all of the study procedures, 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 they 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. If there is any indication that the patient is unable to fully understand and/or retain the information provided, but is indicating consent, their capacity to provide consent will be assessed by the Project Director, a psychiatrist. All procedures and protocols will be approved by the coordinating site KCL Research Ethics Committee, the MGH IRB, the University of Zimbabwe Medical Research Council of Zimbabwe IRB and also the National Research Council of Zimbabwe IRB before study initiation. The Project Director (or designee, in the event of absence) will review all informed consents for accuracy and completeness within one week of their completion.

27. 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, 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 training.

There may be a need to break confidentiality in cases where a participant reveals they are going to seriously harm themselves or someone else, or someone they mention is at serious risk of harm and unable to act for themselves (such as a child, or vulnerable person). In these cases, the researcher or interventionist will first discuss this with their supervisor and/or line manager, and any breaking of confidentiality will be discussed with the participant. Cases may be referred to their usual HIV doctor, local social worker or other agency dependent on local guidance.

Recording of treatment sessions in the PST-AD group will be a required procedure. 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., PIs, 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. Recordings will be maintained until five years after study dissemination in line with the guidelines of the American Psychological Association.

28. Declaration of Interests. The principal investigators do not report any competing interests.

29. Access to Data. The principal investigators, statistician and health economist co-applicant and their designated staff carrying out analyses, and trained study staff will have access to the final trial dataset. Please see Section 31c for plans for further dissemination of data.

30. Ancillary and post-trial care.

Potential Risks to Subjects. 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 questionnaire to be emotionally upsetting and may experience short-term elevations in negative affect during active treatment sessions. As with any study of participants with symptoms of depression, there is always the risk of symptoms worsening. As this is a study of individuals with diagnostic-threshold levels of depression, there is the risk that individuals will report symptoms of depression including the possibility of suicidality.

Participants will be invited to undergo blood draw by venepuncture at baseline, 4, 8 and 12 months. Potential risks to subjects could include bleeding, swelling or bruising at the site of the prick.

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. Please see next section for adequacy of subject protection against risk.

Minimization of risks

Suicide. As part of baseline assessment potential participants will be assessed using the PHQ-9, which includes an item on suicidality. Those who assent to this item will complete the P4 screening tool for active suicide. Participants who do not assent to this item will not complete the P4 screening tool (93). Using this method, those who fall in the category of more than minimal risk will undergo comprehensive assessment for suicidal risk. This will comprise an assessment by the research mental health nurse (RMN). Participants confirmed at risk for suicide attempt will be referred immediately to psychiatric services and not enrolled. The research team will follow up to ensure that the patient has reached services. An electronic record will be kept of all the referrals and will be updated as follow up information is made available. This risk protocol will be adhered to for participants who are enrolled and who indicate suicidal ideation at any point during their study participation. All members of the research team will be trained in this protocol with Standard Operating Procedure (SOP) available for reference.

Treatment procedures. The design of the current study provides for active treatment for depression in the experimental condition, allows for enhanced usual care for depression based on WHO guidelines in the control arm, and monitoring of symptoms in both conditions. The interventions will be implemented by Shona-speaking adherence counsellors 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 depression operationalized for people also managing HIV. All adherence counsellors will also receive training in WHO mhGAP Guidelines for managing depression.

Higher than usual levels of distress. Additional procedures will be in place to further protect participants who may experience higher than usual levels of distress, regardless of treatment

assignment. Adherence counsellors and assessors will be trained by the study Clinical Psychologist and psychiatrist to be vigilant and sensitive to signs of distress in our participants. For those in the treatment condition, the counsellor will re-administer the screening scale for depression at session 6. the stepped-care model ensures that if the score remains above cut-off the counsellor will refer to a nurse with the view of prescribing an antidepressant.

The exclusion criterion prohibiting participants with serious untreated mental illness from participating in the study ensures that those who would be most likely to experience this high level of distress in response to the study procedures are not enrolled.

Increases in depression. For participants in the control condition, if there are increases in depression at study visits, the usual care adherence counsellor will have the option to make appropriate referrals for next-level of care. A trained Community Psychiatric Nurse is available to see patients as part of routine care at Marondera Provincial Hospital, which is one of the study sites. Those in the control condition in whom the adherence counselor or wider treatment team consider needs next-level care have the option of referral to the Community Psychiatric Nurse at Marondera Provincial Hospital or referral to the psychiatric clinic at Chitungwiza CentralHospital. In addition, the site PI and the study Research Mental Health Nurse will either be on-site or on-call and contactable by cell phone. They will provide supervision and additional counselling if required. In the event that inpatient level of care is required it is available at Marondera Provincial Hospital and Chitungwiza Central hospital. In the event that study participants need more than this level of care, transport will be arranged for them to the Tertiary Hospital in the capital by ambulance.

Participants in the intervention arm will have ready access to adherence counsellors and the Research Nurses and the Zimbabwe Programme Manager (who will be on-site much of the time) all of whom are available by cell phone 24 hours a day, 7 days a week. 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 participant’s' welfare.

Blood extraction. With respect to blood extraction, this procedure will be carried out by a trained research assistant or nurses to minimize the accidental injury or discomfort to the participants. Participants who experience harm as a result of this procedure will receive first aid from study staff and referral to medical professional if needed.

Summary of minimization of risks. To emphasize, in the case of treatment non-response or other deterioration or relapse, the adherence counsellors, study nurses, psychologist 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 psychotherapy referrals, arrangements for evaluation in a local Emergency Department, or referrals to hospital outpatient or inpatient levels of care.

For participants who consent to have medical information released from their medical records this information will be restricted to specific medical information related to their HIV disease status and its treatment (current and previous ART regimen, date of treatment initiation, CD4 cell number and HIV viral load during the course of the study), missed HIV care appointments, and concomitant treatment for mood disorders (psychopharmacological or psychotherapeutic, date of initiation of treatment). As both patients with either HIV or mental health problems in

Zimbabwe may experience stigma related to these issues, this information will be safeguarded under the same procedures identified above (Section 27 and 29). Medical record information will be obtained either in person by study personnel or through secure file transfer.

Expected benefits

Although it is possible that there will be no direct benefit to participants in this study, those who participate in this study may benefit from the close monitoring of mood and adherence. Those assigned to the treatment condition may benefit from the intervention provided to treat their depression and support improvements in their ART medication adherence and viral suppression. These potential benefits are provided without charge. Information provided as part of the active and enhanced usual care interventions may help participants better understand their ART enabling them to take it more effectively, and better understand their mood disorder and maintain improvement over the long-term.

Participants in the control condition will have the opportunity to receive the stepped care-AD intervention after 12 months, free of charge. All participants are also provided with a small amount of financial remuneration for completing their participation. We hypothesize that the active treatment will be associated with beneficial effects for both depression and medication adherence and it is anticipated that some of our study participants may reap these benefits.

Participant remuneration

Reimbursement will be given to participants in line with local standards for providing a brief amount of data for clinical session visits. The stepped care-AD intervention arm participants will be asked to attend six clinical sessions, plus a booster session as part of the research study. The EUC control arm participants will be asked to attend two clinical sessions as part of the research study. Although those in the EUC arm will have fewer scheduled clinical sessions, the same total amount will be provided to participants attending all clinical sessions and research assessments in both arms. Table 2 shows the participant reimbursement scheme.

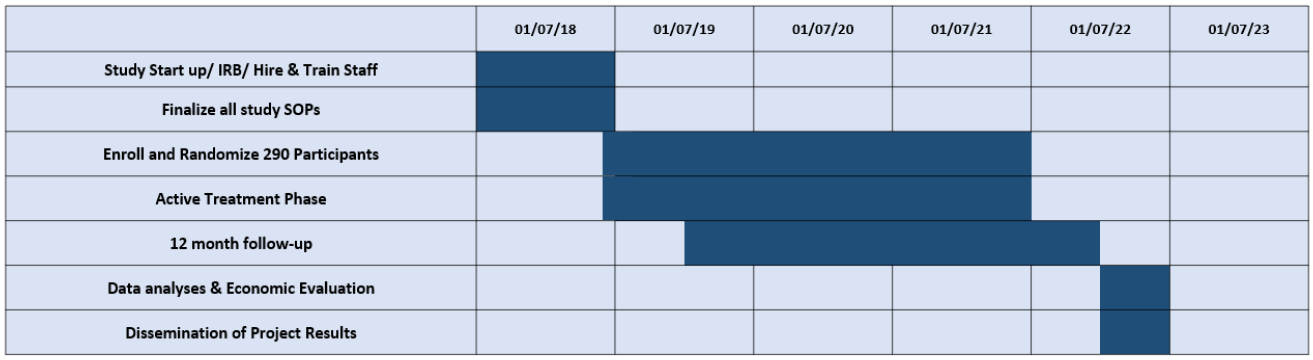
Table 2: Participant Reimbursement Scheme

	Control Arm	Intervention Arm
Baseline Session	1 session @ $6	1 session @ $6
Research Assessment	3 sessions @ $8	3 sessions @ $4
Clinical Session	2 sessions @ $8	6 sessions @ $4
Booster Clinical Session		1 session @ $4
Total	**6 sessions @ $46**	**9 sessions @ $46**

The payment arrangement will be managed through the trial by the research assistants and University of Zimbabwe Programme Manager to maintain blinding.This will mean the independent assessors will not involved in participant reimbursement and therefore are unable to be unblinded by knowledge of reimbursement amount. To reduce attrition, participants will be paid for completing the 4, 8, and 12-month final study assessment (12-month post randomization), as well as for the full baseline assessment. Participant payment is not contingent upon improvement or any other study data at the time of assessment or follow-up.

31a. Dissemination policy

Figure 4 illustrates our approximate expected study timeline for the 5-year study.



Dissemination Policy. Our aim to share our findings with scientists in the field, research participants and Zimbabweans who can influence local policy.

Publishing manuscripts. We plan to publish the findings of this study in peer-reviewed journals. Specifically, our current goals are to publish: (1) a main outcome paper in a journal such as JAMA Psychiatry this paper may also include health economics; (2) a manuscript about our protocol in a publication such as a BMC open access journal; (3) a baseline paper on the correlates of depression and mental health in a journal such as AIDS and Behavior; (4) a paper examining the relationship between depression, treatment adherence, and viral load in a journal such as JCCP or Health Psychology; and (5) a paper on adherence methods in a journal such as AIDS and Behavior or the IAPAC Journal. Manuscripts other than those listed may also be published.

Research Participants: Participants will be given written feedback on the results of the trial. In addition, participants will be invited to dissemination workshops where results of the trial will be verbally explained, and participants will be invited to ask questions. Participants will also be signposted to how they can access study publications.

Scientific Conferences. We plan to present findings from this study at several scientific conferences during year 4 of the project and a year after the project is set to end. At the moment, we plan to present our findings at the IAPAC Conference in Miami, Florida, the IAS Conference on HIV Science and at CROI. Additionally, we also plan to look into presenting our findings at a global mental health conference.

Local stakeholders meeting. We plan to disseminate our results to people in Zimbabwe who may directly benefit from our findings. Specifically, we plan to present our findings at stakeholder meetings in years 4 and 5 of the project. Attendees at these meetings will include Ministry of Health officials, providers and workers at clinics, service users and advocates. Additionally, we also plan to present our findings at community advisory boards.

ClinicalTrials.gov. We will ensure that the study is registered on ClinicalTrials.gov, that the results information is submitted to ClinicalTrials.gov as outlined in the policy and according to

the specific timelines stated in the policy, and that all registration information and results information is up to date. Specifically, the study will be registered on ClinicalTrials.gov before the first subject is enrolled and will be updated once every 12 months at the very minimum. Summary results will also be reported less than a year after trial completion. All ClinicalTrials.gov responsibilities will be managed by Dr. Melanie Abas and study staff at King's College London, the study's coordinating site. In addition, all informed consent documents in this study will include a specific statement relating to the posting of clinical trials information on ClinicalTrials.gov. Please note that since this study does not evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration, it is not an Applicable Clinical Trial (ACT). Therefore, it is subject to the NIH Policy on Dissemination of NIH Funded Clinical Trial Information, but not FDAAA 801 as implemented by 42 CFR Part 11 (the Final Rule). King's College London policy (KHP-CTO SOP 12 'Application and Maintenance of a CTA') details the legislative requirement for publication in line with NIH policy, which states the study results will be reported no later than 12 months from end of trial declaration.

31b. The principal investigators, and other investigators involved with this project, will be involved in paper authorship. There are no plans to use professional writers.

31c. We plan to make an annotated dataset available to scientists working in the field who want to do secondary data analysis. We will make this dataset available once the parent research team (including researchers in the United Kingdom, United States, and Zimbabwe) has finished their planned primary and secondary analyses.

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