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Task-sharing with lay counsellors to deliver a stepped care intervention to improve depression, antiretroviral therapy adherence, and viral suppression in people living with HIV: study protocol for the TENDAI randomised controlled trial.

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*Professor James Hakim was involved in the TENDAI study and this manuscript up until his death in 2020

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Abstract

Introduction: Non-adherence to antiretroviral therapy (ART) is the main cause of viral non-suppression and its risk is increased by depression. In countries with high burden of HIV there is a lack of trained professionals to deliver depression treatments. This paper describes the protocol for a 2-arm parallel group superiority 1:1 randomised controlled trial, to test the effectiveness and cost-effectiveness of the TENDAI stepped care task-shifted intervention for depression, ART non-adherence, and HIV viral suppression delivered by lay interventionists. Methods and Analysis: Two hundred and ninety people living with HIV (PLHIV) aged ≥18 years who meet criteria for depression (Patient Health Questionnaire =>10) and viral non-suppression (=> 1000 HIV copies per ml) are being recruited from HIV clinics in towns in Zimbabwe. The intervention group will receive a culturally adapted 6-session psychological treatment including problem-solving therapy, positive activity scheduling, skills to cope with stress and poor sleep, and content to target barriers to non-adherence to ART. Participants with persistent depression step up to a nurse-evaluation for antidepressant medication. The control group receives usual care for viral non-suppression, consisting of three sessions of adherence counselling from existing clinic staff, and enhanced usual care for depression in line with the WHO Mental Health Gap intervention guide. The primary outcome is viral suppression (<1000 HIV copies per ml) at 12 months post-randomisation. Ethics and Dissemination: The study and its tools were approved by MRCZ/A/2390 in Zimbabwe and RESCM-18/19-5580 in the United Kingdom. Study findings will be shared through the community advisory group, conferences, and open access publications.

Strengths and Limitations:

Strengths:

- The first randomised controlled trial in a low-income country to test an intervention to improve both adherence to antiretroviral therapy and depression in people living with HIV.
- Culturally adapted and culturally appropriate intervention to address barriers to adherence to antiretroviral therapy and to treat depression, based on extensive preliminary work.
- Cost-effectiveness under investigation.
- Stepped care intervention be delivered through task-shifting to non-specialist staff, allowing for future scale up.

Limitation:

- Limited scope to assess implementation science questions given the individually randomised design.

Introduction

Over 27% of people in sub-Saharan Africa currently receiving antiretroviral therapy (ART) are non-adherent (1), and non-adherence to ART is the main cause of viral non-suppression (2). Depression is among the strongest correlates of non-adherence and affects over 15% of PLHIV attending HIV out-patient clinics in sub-Saharan Africa (1, 3, 4). Depression is linked to non-adherence through the reduced motivation and forgetting to take ART (5), through impaired problem-solving ability (6), and through interfering with uptake of existing adherence support programs. Depression may also impact adherence through its association with structural factors, such as poverty, and interpersonal difficulties which impede access to HIV medication (5, 7, 8). Non-adherence to ART may also precede and increase risk of depression (9).

Countries with high burden of HIV, such as Zimbabwe, have a dearth of trained mental health professionals. Given the public health importance of viral suppression (10), and the strong association with depression, adherence interventions must address comorbid psychological factors and be able to be delivered through task-shifting to non-specialists (11). Systematic reviews of mental health interventions in PLHIV in low resource settings have been unable to report effects on HIV outcomes as, to date, these have not been studied (12, 13).

The most promising evidence for the effectiveness and utility of integrated treatments for

depression and ART adherence for PLHIV has come from the development of Cognitive Behavioural Therapy for Adherence and Depression (CBT-AD) in the United States (14, 15). CBT-AD, which includes the "Life Steps" intervention for addressing barriers to medication adherence, has been shown to improve rates of ART adherence, and to reduce depression severity among men in the US (16 , 17). In contrast, interventions for PLWH with depression and poor adherence which *only* target mood have not been found to improve viral suppression (18). Recent reports, including from our team in Zimbabwe, support the acceptability and feasibility of culturally-adapted CBT-AD for low resource settings (19-21). However, there have yet to be any definitive RCTs from low resource settings focused on treatment of depression and ART adherence to improve viral suppression (22). Thirteen percent of the adult population in Zimbabwe is living with HIV, with 22% of those virally non-suppressed (22). The objective of this trial is to test the effectiveness and cost-effectiveness of the TENDAI stepped care psychological intervention for adherence to ART and depression, (Stepped Care-AD), compared to enhanced usual care, for PLHIV in Zimbabwe with viral non-suppression and depression.

Methods and Analysis

Study Design and Setting

The study is a two-arm parallel group superiority 1:1 randomised effectiveness trial (n=290). PLHIV receive care according to the standard national guidelines (23). Viral load is monitored every 12 months, with more frequent screening every 3 months for those who are virally non-suppressed. Participants are being recruited from two sites in Zimbabwe providing HIV services for those initiated on ART. These are the Marondera Provincial Hospital, and Chitungwiza Central Hospital, along with satellite clinics for each hospital. Marondera is the capital of Mashonaland East province, situated in the north east of Zimbabwe. The town and its

surrounding district have a total population of approximately 224,000 (24). Chitungwiza is an urban town, divided into five townships, with a total population of approximately 391,000 (25). Taken together, both sites combined have approximately 25,000 adults registered as receiving ART.

Patient and Public Involvement

No patient involvement in the design of the study. Results will be disseminated to study participants and community members via local advisory groups.

Eligibility Criteria

Inclusion criteria: 1) HIV positive and initiated on ART for at least 6 months; 2) clinically significant depression symptoms (operationalised as a score of 10 or more on the locally validated Patient Health Questionnaire (PHQ-9) (4); 3) virally non-suppression in the past 2 months (viral load >/= 1000 copies/mL); 4) able to provide informed consent ; and 5) if prescribed anti-depressants, be on a stable regimen for at least 2 months. Exclusion criteria: 1) unwilling or unable to provide informed consent; 2) major untreated or undertreated mental illness (e.g. untreated psychosis or mania, actively suicidal), major or advanced physical disease or severe cognitive impairment which would interfere with engagement in Stepped Care-AD; 3) have received a course of problem solving therapy or cognitive-behavioural psychological therapy for depression; or 4) <18 years old.

Study Procedures

Recruitment and Informed Consent

Research Assistants (RAs) in the ART clinic approach patients identified by clinic staff as having a detectable viral load (>1000 copies/mL) in the past 2 months or at high risk of viral non-suppression, e.g self-reported poor adherence. Potentially eligible individuals will complete a brief screen for inclusion and exclusion criteria. Those meeting initial screening eligibility criteria are invited to complete informed consent procedures and the full baseline assessment. Informed consent will include consent to access participants' medical records, and for telephone calls and home visits if needed for follow-up. Capacity to provide consent is assessed by a licensed psychiatrist (WM) for any participant indicating consent but suspected of being unable to fully understand and/or retain information provided.

Baseline

A trained RA collects data by face-to-face interview including: demographics, HIV characteristics, measures of socio-economic position (26, 27), depression using the Patient Health Questionnaire (PHQ-9) (4), anxiety using the Hospital Anxiety and Depression Scale (28) quality of life using The EQ-5D-3L (29), use of alcohol and substances (30, 31), cognitive impairment using the International HIV Dementia Scale (32), psychiatric diagnosis using the MINI International Neuropsychiatric Interview (33), use of health services in the last 4 months using a modified version of the Client Services Receipt Inventory (31) and several additional exploratory measures.

Viral load in the past 60 days is ascertained from the participants medical records, or, for those who have not been tested in the past two months, by testing plasma. Current ART regimen and recent CD4 test results are taken from participants medical records. A blood sample for dried blood spot (DBS) is used to detect the presence of ART medications (34).

Eligibility

The study team, including a clinical psychologist or psychiatrist, will meet weekly via teleconference to discuss each baseline assessment and confirm that participants meet eligibility criteria.

Randomisation

Approximately 2 weeks after the baseline assessment, eligible participants return for a randomisation visit and are randomly assigned to Stepped Care-AD or enhanced usual care (EUC). Randomisation is determined by a computer-generated chart and is conducted via the REDCap randomisation module by the Zimbabwe site Programme Manager.

Follow-Up Assessments

In addition to baseline, there are 3 major study assessments: 4-, 8-, and 12-months post-randomisation. An Independent Assessor (IA) who is blind to study condition will administer the PHQ-9, EQ-5D-3L, and self-report medication adherence measures. RAs will collect self-report data including use of alcohol and substances (30, 31), Hospital Anxiety and Depression Scale for Anxiety (28), quality of life (29), and use of other health care services (35) . 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. Participants without a viral load test in the past 30 days are invited to undergo venepuncture for viral load testing, which is in addition to the venepuncture for ART detection.

Interventions

Active Intervention Arm: Task-sharing Stepped Care Intervention for Adherence and Depression (TENDAI Stepped Care-AD).

As shown in Figure 1, all participants in the TENDAI arm receive six 50-minute sessions of a culturally adapted intervention for depression and non-adherence to ART, followed by one booster session six weeks later. The intervention is based on cognitive behavioural principles and includes problem-solving therapy, positive activity scheduling, skills to cope with stress and poor sleep, and content to target barriers to non-adherence to ART. Training of interventionists emphasises common elements of effective psychological interventions including empathy, active listening, and creating realistic hope (36).

A) Adherence to antiretroviral therapy. Session 1 comprises a locally adapted version of the Lifesteps adherence intervention called *Nzira Itsva* (14, 37). This includes motivation, goal setting, video-based education and problem solving. Motivational interviewing is used to identify the participants life goals and to tie adherence to achieving these goals. Education about on time adherence is provided using an animated video in the Shona language. Barriers to adherence are assessed through a culturally adapted checklist. During each of the subsequent sessions 2-6 targeting depression, 5- to 10-minute adherence boosters are included to review adherence to ART and the participants' experience with strategies to overcome barriers to adherence.

B) Psychological intervention for depression. Sessions 2 and 3 focus on psychoeducation about depression and problem-solving therapy (PST) (38), incorporating storytelling and illustrations, and training in problem-solving. A goal for each session is to identify a defined specific problem to work on, to collaboratively agree a solution to work on and to schedule homework. An intervention based on PST has been shown to be acceptable and effective for depression in Zimbabwe (39, 40). In Session 4 participants are encouraged to choose and

schedule at least four adaptive activities in which to engage: an activity that promotes a sense of achievement, a physical activity, a pleasurable activity, and a social activity. Homework is mutually agreed as part of every session, to test out participants' implementation of solutions to problems, and of positive activities. Thorough review of homework is done at each session, including barriers to doing homework. Skills to promote good sleep and relaxation are taught in Sessions 5 and 6. A relapse prevention plan is developed in session 6 including triggers for relapse of depression, warning signs, coping strategies and self-care activities. Fidelity of the intervention will be assessed through rating 10% of audio-recorded sessions for adherence to the intervention protocol and for therapist competence (41).

C) Booster session. About six weeks after the sixth session, participants are invited to a 50-minute booster session. This includes a review of depressive symptoms, and of adherence to HIV treatment and, where appropriate, adherence to antidepressant medication. The session includes ongoing positive activity scheduling to promote recovery from depressive symptoms.

D) Stepped up care. Participants with persistent depression after at least 4 sessions receive step up to a nurse-evaluation for antidepressant medication. The antidepressant Fluoxetine is offered for those with confirmed depression.

Control Arm: Enhanced Usual Care (EUC)

All participants in the control arm receive Enhanced Usual Care (EUC) comprising usual care for viral non-suppression, and enhanced usual care for depression in line with the WHO Mental Health Gap intervention guide. Usual care for those with viral non-suppression includes three sessions of adherence counselling provided by an adherence counsellor, nurse, or NGO support worker based at the clinic. These sessions include establishing the participants

knowledge about HIV and ART, providing information about use of ART, encouraging adherence, and describing barriers to adherence. Strategies commonly used include encouraging use of an alarm and a treatment supporter, linking ART taking to daily routines, and disclosure of HIV status. The first session is given on the day of receiving viral load results, with two subsequent sessions scheduled on a monthly basis. Referrals may be made to local support groups or organisations for social or economic support, general psychological support or to an HIV clinician. The HIV operational strategy recommends that all patients living with HIV and registered at facility should be screened for common mental disorders (CMD) annually. Patients with high viral load or those initiating ART should be screened for CMD at their appointment (42). Patients exhibiting symptoms of common mental disorders or psychological distress should be managed with counselling interventions and are usually referred to the outpatient's department to be assessed by a Psychiatric nurse. If they require further treatment, they will be seen by a psychiatrist. Patients can also be referred to community-based organization to receive psychosocial services (42). Usual care for depression is enhanced in three ways: 1) The study team will train all health service providers in the study sites on psychological and antidepressant management of depression using the WHO Mental Health Gap intervention guide (mhGAP) (43); 2) we will provide a letter for each participant communicating diagnosis of depression to their HIV-care provider; and 3) we will provide those in the EUC condition with access to Stepped Care-AD upon completion of their 12-month follow-up visit.

Outcomes

Primary Outcome

Viral suppression at 12-months post-randomisation follow-up (defined as <1000 copies/mL), measured through blood (plasma). This measure will be taken from the medical

record if viral load was collected 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 randomisation measured as the total score on the Patient Health Questionnaire (PHQ-9) (4).
2. Adherence to ART medication at 4-, 8-, and 12-months post randomisation assessed as the proportion of the sample achieving at least 90% adherence in the past month assessed through pharmacy refill (44).
3. Self-reported adherence to ART medication at 4-, 8-, and 12-months post randomisation assessed as the frequency of adherence in the past 30 days (45).
4. Viral load copies/mL at 12-months post-randomisation follow-up measured as mean log Viral Load.

Tertiary Outcomes

The total costs of the health care services used by each study participant will be calculated using service use information collected from hospital records and from participant self-report (via a modified version of the Client Services Receipt Inventory suitable for use in sub-Saharan Africa (35)) at 4-, 8-, and 12-month follow-up and with unit costs identified and calculated using locally available data. Detailed information on the use of Stepped Care-AD and EUC will be collected from therapist records. Quality of life at 4, 8 and 12 months is measured using EQ-5D-3L (29). Quality-adjusted life years will be calculated using Zimbabwe-specific health states (34).

Data Collection and Management

Trial data is collected and stored in REDCap, a data management tool designed for collection and protection of patient health information. The REDCap database is hosted and routinely audited at Massachusetts General Hospital (MGH), with access restricted via user roles. Data extracts are sent to the study statisticians, via secure file transfer. To ensure accuracy of collected data, MGH staff generate weekly error reports. These error reports are then sent to staff in Zimbabwe, who correct any discrepancies and document changes made to the database.

Strategies to Improve Participant Retention

Procedures to maximise participant retention include reimbursing participants for attending study visits (equal amount in both arms), sending text message reminders before scheduled appointments and collection of locator information (e.g., contact information of two significant others with whom the participant is in regular contact). 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. Where participants are unable to travel to the clinic to complete follow up assessments (e.g. because of COVID-19 lockdown travel restriction), participants will be offered phone assessments. Where participants can not be reached by phone, a home visit may be conducted.

Ethics

All study procedures were reviewed and approved by ethics committees at King's College London (RESCM-17/18-5580), Massachusetts General Hospital (IRB00012706), and the Medical Research Council of Zimbabwe (MRCZ/A/2390). SAEs will be reported to research ethics committees at King's College London, MGH, and the Medical Research Council of Zimbabwe within 72 hours.

Confidentiality

Participants are given a study-specific identification number at screening that is used on all forms and data collection instruments, excluding the consent form. participants are referred to only by their identification number during eligibility and supervision meetings. A file that links participant names to identification numbers is stored in a locked file at the University of Zimbabwe.

Blinding

To reduce bias and maximise the validity of the findings, the Independent Assessor (IA) for the primary and secondary outcomes, and the lead study statistician, is blinded to randomisation condition. To ensure blinding, the IA will explain their role to participants and ask that they do not give the IA information about the treatment they received. The lead study statistician will not attend meetings where randomisation or clinical issues are discussed, and their access in REDCap is restricted so that they cannot view any data or report that may unblind them. A second statistician, who will conduct the analyses and will review data for thoroughness and completeness, will not be blinded. This trial does not have procedures for unblinding IAs or the lead study statistician. If the IA is concerned about the safety of a participant, they will communicate the concern to study staff, who will contact the clinical supervisor.

Data Safety and Monitoring Board (DSMB)

A DSMB, consisting of members with experience in clinical trials for mental disorders, biostatistics, HIV in African settings, and human subject protection issues will function independent of the sponsor and monitor safety of study participants and integrity of data. The DSMB will meet annually and receive safety information in an unblinded manner. Expedited review by the DSMB will occur for all serious adverse events (SAE) as defined as any fatal,

immediately life-threatening, or substantially disabling event; event requiring or prolonging inpatient hospitalisation, or any congenital anomaly.

Statistical Methods

Sample Size

Using two-sided Fisher's exact test, $\alpha = 0.05$ and 20% attrition, 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. Pilot data showed a larger difference between arms (50% in the EUC arm vs. 75% in the intervention arm) (20), suggesting this should be a conservative sample size estimate.

Statistical Methods for Primary and Secondary Outcomes

Baseline and outcome variables will be summarised using appropriate statistics; no baseline statistical comparisons will be made. The main analysis will follow intention to treat principles as much as possible, reporting appropriate 95% confidence intervals and use a 5% significance level. All models will include a site stratification variable. In the mixed models we will have random intercepts at the participant level, and random slopes if warranted (assessed via likelihood ratio test).

Twelve-month primary outcome viral load will be coded as suppressed (<1000 copies/mL) vs not suppressed (>=1000 copies/mL). Where these data are missing, the individual has died, and medical or death records indicate death due to high viral load/death was AIDS related, they will be coded as not suppressed, otherwise the outcome will be left missing. Suppressed/not suppressed will be the dependent variable in a logistic regression model estimating the TENDAI vs EUC odds ratio (OR), with trial arm as the independent variable. The

mean difference in PHQ-9 depression and self-report adherence will each be estimated using a linear mixed effects model with the 4-, 8- and 12-month measures as dependent variables, with the baseline measure of the outcome, time, and trial arm by time interaction terms as independent variables. The OR at 4, 8 and 12 months for ≥90% adherence vs＜90% adherence by pharmacy refill in the past 30 days will be estimated using a logistic mixed effects model with the 4, 8 and 12-month measures as dependent variables, and independent variables as described for PHQ-9 and self-report adherence. The mean difference in log copies/mL of viral load at 12 months will be estimated using a linear regression model with log viral load at 12 months as the dependent variable, trial arm and baseline log viral load as independent variables.

A "per protocol" analysis for the primary viral load outcome only will exclude participants not completing at least four TENDAI sessions, and anyone found to be ineligible post randomisation. No interim or formal powered subgroup analyses are planned, however, we will explore moderation by sex for viral suppression, self-report adherence and depression outcomes by adding a sex by trial arm (by time, where appropriate) interaction term to the final outcome analysis models. Additional exploratory mediation analysis is planned, but will not be reported on in the main paper. Missing baseline measures will be imputed using simple mean imputation (46). Missing repeatedly measured outcome data will be handled using mixed models/maximum likelihood methods, including baseline variables predicting missing outcome data. If there is more than 10% missing primary outcome data and post-randomisation variables (completion of therapy in the TENDAI arm only and ART adherence at 12 months) predict whether these data are missing, we will consider multiple imputation (MI) (47).

Cost-effectiveness results will be reported following CHEERS guidelines (48). First, the mean average total cost in each randomised 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 (49). 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 (50). 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.

Dissemination

Dissemination of findings will involve three primary papers describing the study outcomes, as well as submitting to lead workshops on the treatment approach at relevant national meetings and conferences. Additionally, data will be available to external parties after publication of the outcome papers via PI-approved application. Data will be stored indefinitely.

Discussion

In Zimbabwe, both HIV and co-morbid depression are common, yet, as in other low-resource settings with high HIV burden, there is a lack of evidence on interventions to improve both ART adherence and depression (51, 52). Due to resource limitations, interventions that

allow for task-shifting and administration by community health workers are particularly well-placed to be effective and sustainable. Our treatment, Stepped Care-AD, blends active ingredients of treatment for depression with a culturally-adapted LifeSteps intervention to enhance adherence to ART (20, 37). If successful, the Stepped Care-AD intervention represents a useful model for policy and for further research. As the primary outcome of the trial is viral suppression, its implementation in Zimbabwe and other low-resource settings may further the UNAIDS goal of ending the AIDS epidemic by 2030, through optimising viral suppression (53). Results gathered in a Zimbabwean context may be leveraged for testing and implementation of similar task-shifted stepped care interventions in other Sub-Saharan African settings.

Trial Status

This trial began recruitment and enrolment on 2nd July 2019.

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Figure 1: Stepped Care-AD Flow

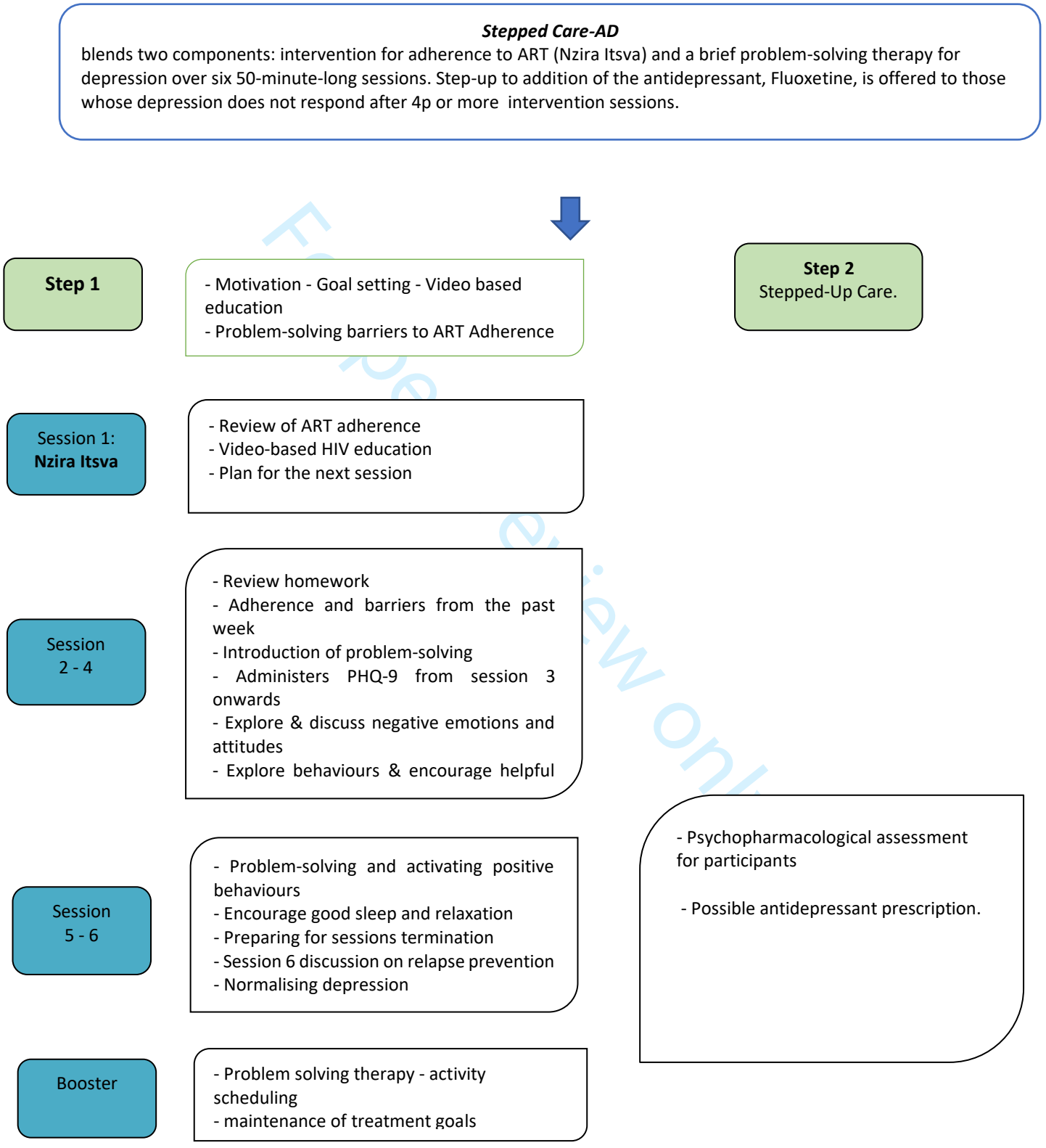
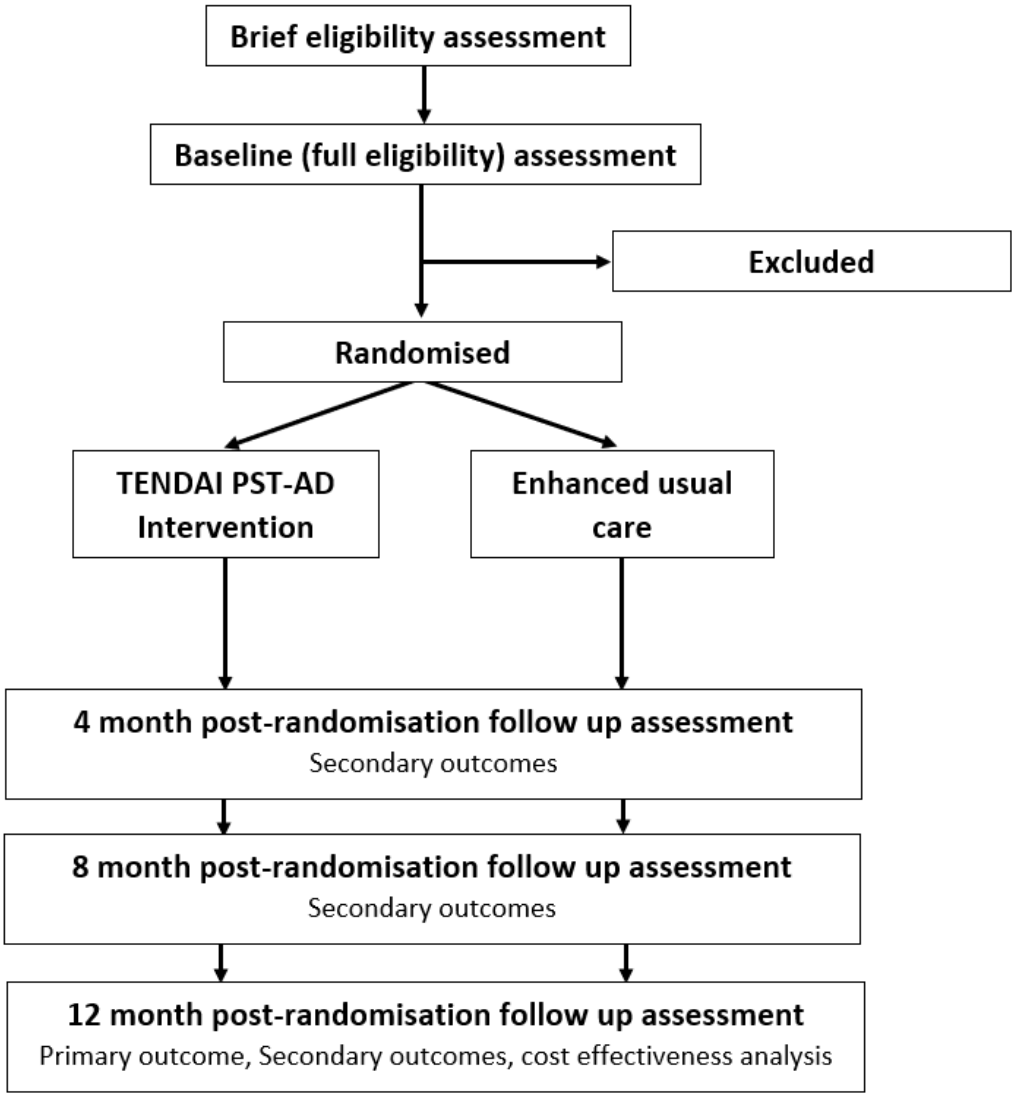


Figure 2: Participant Flow



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11, 19
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8, 20

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 12-13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13-14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12, 14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 6
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Task-sharing with lay counsellors to deliver a stepped care intervention to improve depression, antiretroviral therapy adherence, and viral suppression in people living with HIV: study protocol for the TENDAI randomised controlled trial.

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Task-sharing with lay counsellors to deliver a stepped care intervention to improve depression, antiretroviral therapy adherence, and viral suppression in people living with HIV: study protocol for the TENDAI randomised controlled trial.

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Roles of Contributors

*Professor James Hakim was involved in the TENDAI study and this manuscript up until his death in 2020

Melanie Abas: Professor Abas is the King's College London PI for the trial and engaged in substantial writing of this manuscript and gaining funding for the study.
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Conall O'Cleirigh: Dr. O'Cleirigh is the Massachusetts General Hospital PI for the trial and engaged in substantial writing of this manuscript and assisted in gaining funding for the study.
Sponsor: The National Institute of Mental Health provides funding for this trial and monitors progress on the project through yearly Research Performance Progress Reports.

Abstract

Introduction: Non-adherence to antiretroviral therapy (ART) is the main cause of viral non-suppression and its risk is increased by depression. In countries with high burden of HIV

there is a lack of trained professionals to deliver depression treatments. This paper describes the protocol for a 2-arm parallel group superiority 1:1 randomised controlled trial, to test the effectiveness and cost-effectiveness of the TENDAI stepped care task-shifted intervention for depression, ART non-adherence, and HIV viral suppression delivered by lay interventionists. Methods and Analysis: Two hundred and ninety people living with HIV (PLHIV) aged ≥18 years with probable depression (Patient Health Questionnaire =>10) and viral non-suppression (=> 1000 HIV copies per ml) are being recruited from HIV clinics in towns in Zimbabwe. The intervention group will receive a culturally adapted 6-session psychological treatment (PST-AD) including problem-solving therapy, positive activity scheduling, skills to cope with stress and poor sleep, and content to target barriers to non-adherence to ART. Participants whose score on the PHQ-9 remains >=10, and/or falls by less than 5-points, step up to a nurse-evaluation for possible antidepressant medication. The control group receives usual care for viral non-suppression, consisting of three sessions of adherence counselling from existing clinic staff, and enhanced usual care for depression in line with the WHO Mental Health Gap intervention guide. The primary outcome is viral suppression (<1000 HIV copies per ml) at 12 months post-randomisation. Ethics and Dissemination: The study and its tools were approved by MRCZ/A/2390 in Zimbabwe and RESCM-18/19-5580 in the United Kingdom. Study findings will be shared through the community advisory group, conferences, and open access publications.

Strengths and Limitations:

Strengths:

- The first randomised controlled trial in a low-income country to test an intervention to improve both adherence to antiretroviral therapy and depression in people living with HIV.
- Culturally adapted and culturally appropriate intervention to address barriers to adherence to antiretroviral therapy and to treat depression, based on extensive preliminary work.

- Assessment of the cost-effectiveness of the TENDAI stepped care task-shifted intervention
- Stepped care intervention is delivered through task-shifting to non-specialist staff, allowing for future scale up.

Limitation:

- Limited scope to assess implementation science questions given the individually randomised design.

Introduction

Over 27% of people in sub-Saharan Africa currently receiving antiretroviral therapy (ART) are non-adherent (1), and non-adherence to ART is the main cause of viral non-suppression (2). Achieving and maintain viral suppression is not only an effective HIV treatment strategy but also an effective HIV prevention approach, preventing transmission of the virus to sexual partners, and from mother to child (3, 4). Depression is among the strongest correlates of non-adherence and affects over 15% of PLHIV attending HIV out-patient clinics in sub-Saharan Africa (1, 5, 6). Depression is linked to non-adherence through the reduced motivation and forgetting to take ART (7), through impaired problem-solving ability (8), and may interfere with uptake of existing adherence support programs. Depression may also impact adherence through its association with structural factors, such as poverty, and interpersonal difficulties which impede access to HIV medication (7, 9, 10). Non-adherence to ART may also precede and increase risk of depression (11). Evidence-based interventions for depression include psychological interventions based on cognitive behavioural approaches, and antidepressant medication (12)

Countries with high burden of HIV, such as Zimbabwe, have a dearth of trained mental health professionals. Given the public health importance of viral suppression (13), and the strong association with depression, adherence interventions must address comorbid psychological factors and be able to be delivered through task-shifting to non-specialists (14). Systematic reviews of mental health interventions in PLHIV in low resource settings have been unable to

report effects on HIV outcomes as, to date, these have not been studied (15, 16).

The most promising evidence for the effectiveness and utility of integrated treatments for depression and ART adherence for PLHIV has come from the development of Cognitive Behavioural Therapy for Adherence and Depression (CBT-AD) in the United States (17, 18). CBT-AD, which includes the "Life Steps" intervention for addressing barriers to medication adherence, has been shown to improve rates of ART adherence, and to reduce depression severity among men in the US (19 , 20). In contrast, interventions for PLWH with depression and poor adherence which *only* target mood have not been found to improve viral suppression (21). Recent reports, including from our team in Zimbabwe, support the acceptability and feasibility of culturally-adapted cognitive behavioural interventions for low resource settings (22-24). However, there have yet to be any definitive RCTs from low resource settings focused on treatment of depression and ART adherence to improve viral suppression (25). Thirteen percent of the adult population in Zimbabwe is living with HIV, with 22% of those virally non-suppressed (22). The objective of this trial is to test the effectiveness and cost-effectiveness of the TENDAI stepped care psychological intervention for adherence to ART and depression, (Stepped Care-AD), compared to enhanced usual care, for PLHIV in Zimbabwe with viral non-suppression and depression. TENDAI is derived from principles of problem-solving and psychoeducation for depression and adherence, and motivational interviewing.

Methods and Analysis

Study Design and Setting

The study is a two-arm parallel group superiority 1:1 randomised effectiveness trial (n=290). PLHIV receive care according to the standard national guidelines (26). Viral load is monitored every 12 months, with more frequent screening every 3 months for those who are

virally non-suppressed. Participants are being recruited from two sites in Zimbabwe providing HIV services for those initiated on ART. These are the Marondera Provincial Hospital, and Chitungwiza Central Hospital, along with satellite clinics for each hospital. Marondera is the capital of Mashonaland East province, situated in the north east of Zimbabwe. The town and its surrounding district have a total population of approximately 224,000 (27). Chitungwiza is an urban town, divided into five townships, with a total population of approximately 391,000 (28). Taken together, both sites combined have approximately 25,000 adults registered as receiving ART.

Patient and Public Involvement

No patient involvement in the design of the study. Results will be disseminated to study participants and community members via local advisory groups.

Eligibility Criteria

Inclusion criteria: 1) HIV positive and initiated on ART for at least 6 months; 2) clinically significant depression symptoms (operationalised as a score of 10 or more on the locally validated Patient Health Questionnaire (PHQ-9) (6); 3) virally non-suppressed in the past 2 months (viral load >/= 1000 copies/mL); 4) able to provide informed consent ; and 5) if prescribed anti-depressants, have been on a stable anti-depressant regimen for at least 2 months. Exclusion criteria: 1) unwilling or unable to provide informed consent; 2) major untreated or undertreated mental illness (e.g. untreated psychosis or mania, actively suicidal assessed using the MINI and P4 suicide screener), major or advanced physical disease (assessed using clinic records) or severe cognitive impairment (assessed using the International HIV dementia scale) which would interfere with engagement in Stepped Care-AD; 3) have received a course of

problem solving therapy or cognitive-behavioural psychological therapy for depression; or 4) <18 years old.

Study Procedures

Recruitment and Informed Consent

See Figure 1 for study flow. Research Assistants (RAs) in the ART clinic approach patients identified by clinic staff as having a detectable viral load (>1000 copies/mL) in the past 2 months or at high risk of viral non-suppression, e.g., self-reported poor adherence. Potentially eligible individuals will complete a brief screen for inclusion and exclusion criteria. Those meeting initial screening eligibility criteria are invited to complete informed consent procedures and the full baseline assessment. Informed consent will include consent to access participants' medical records, and for telephone calls and home visits if needed for follow-up. Capacity to provide consent is assessed by a licensed psychiatrist (WM) for any participant indicating consent but suspected of being unable to fully understand and/or retain information provided.

Baseline

A trained RA collects data by face-to-face interview including: demographics, measures of socio-economic position (employment status, educational history, and ownership of household assets) (29, 30), depression using the Patient Health Questionnaire (PHQ-9) (6), anxiety using the Hospital Anxiety and Depression Scale (31) quality of life using The EQ-5D-3L (32), use of alcohol and substances (33, 34), cognitive impairment using the International HIV Dementia Scale (35), psychiatric diagnosis using the MINI International Neuropsychiatric Interview (36), use of health services in the last 4 months using a modified version of the Client Services Receipt Inventory (31) and several additional exploratory measures.

Viral load in the past 60 days is ascertained from the participants medical records, or, for those who have not been tested in the past two months, by testing plasma. Current ART regimen and recent CD4 test results are taken from participants medical records. A blood sample for dried blood spot (DBS) is used to detect the presence of ART medications (37).

Eligibility

The study team, including a clinical psychologist or psychiatrist, will meet weekly via teleconference to discuss each baseline assessment and confirm that participants meet eligibility criteria.

Randomisation

Approximately 2 weeks after the baseline assessment, eligible participants return for a randomisation visit and are randomly assigned to Stepped Care-AD or enhanced usual care (EUC). Randomisation is determined by a computer-generated chart and is conducted via the REDCap randomisation module by the Zimbabwe site Programme Manager.

Follow-Up Assessments

In addition to baseline, there are 3 major study assessments: 4-, 8-, and 12-months post-randomisation. An Independent Assessor (IA) who is blind to study condition will administer the PHQ-9, EQ-5D-3L, and self-report medication adherence measures. RAs will collect self-report data including use of alcohol and substances (33, 34), Hospital Anxiety and Depression Scale for Anxiety (31), quality of life (32), and use of other health care services (38) . 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. Participants without a viral load test in the past 30 days are invited to undergo venepuncture for viral load testing, which is in addition to the venepuncture for ART detection.

Interventions

Active Intervention Arm: Task-sharing Stepped Care Intervention for Adherence and Depression (TENDAI Stepped Care-AD).

As shown in Figure 2, all participants in the TENDAI arm receive six 50-minute sessions of a culturally adapted intervention for depression and non-adherence to ART delivered weekly, followed by one booster session six weeks later. The intervention is based on cognitive behavioural principles and includes problem-solving therapy, positive activity scheduling, skills to cope with stress and poor sleep, and content to target barriers to non-adherence to ART. Training of interventionists delivered by expert clinicians emphasises common elements of effective psychological interventions including empathy, active listening, and creating realistic hope (39).

A) Adherence to antiretroviral therapy. Session 1 comprises a locally adapted version of the Lifesteps adherence intervention called *Nzira Itsva* (17, 40). This includes motivation, goal setting, video-based education and problem solving. Motivational interviewing is used to identify the participants' life goals and to tie adherence to achieving these goals. Education about on time adherence is provided using an animated video in the Shona language. Barriers to adherence are assessed through a culturally adapted checklist. During each of the subsequent sessions 2-6 targeting depression, 5- to 10-minute adherence boosters are included to review adherence to ART and the participants' experience with strategies to overcome barriers to adherence.

B) Psychological intervention for depression. Sessions 2 and 3 focus on psychoeducation about depression and problem-solving therapy (PST) (41), incorporating storytelling and illustrations, and training in problem-solving. A goal for each session is to identify a defined specific problem to work on, to collaboratively agree a solution to work on and to schedule

homework. An intervention based on PST has been shown to be acceptable and effective for depression in Zimbabwe (42, 43). In Session 4 participants are encouraged to choose and schedule at least four adaptive activities in which to engage: an activity that promotes a sense of achievement, a physical activity, a pleasurable activity, and a social activity. Homework is mutually agreed as part of every session, to test out participants' implementation of solutions to problems, and of positive activities. Thorough review of homework is done at each session, including barriers to doing homework. Skills to promote good sleep and relaxation are taught in Sessions 5 and 6. A relapse prevention plan is developed in session 6 including triggers for relapse of depression, warning signs, coping strategies and self-care activities. Fidelity of the intervention will be assessed through rating 10% of audio-recorded sessions for adherence to the intervention protocol and for therapist competence (44).

C) Booster session. About six weeks after the sixth session, participants are invited to a 50-minute booster session. This includes a review of depressive symptoms, and of adherence to HIV treatment and, where appropriate, adherence to antidepressant medication. The session includes ongoing positive activity scheduling to promote recovery from depressive symptoms.

D) Stepped up care. Participants with persistent depression (depression score continuing above cut-off (PHQ-9 >=10) or if they have less than a 5-point improvement in PHQ-9 score) after at least 4 sessions receive step up to a nurse-evaluation for antidepressant medication. The antidepressant Fluoxetine is offered for those with confirmed depression.

Control Arm: Enhanced Usual Care (EUC)

All participants in the control arm receive Enhanced Usual Care (EUC) comprising usual care for viral non-suppression, and enhanced usual care for depression in line with the WHO Mental Health Gap intervention guide. Usual care for those with viral non-suppression includes

three sessions of adherence counselling provided by an adherence counsellor, nurse, or NGO support worker based at the clinic. These sessions include establishing the participants knowledge about HIV and ART, providing information about use of ART, encouraging adherence, and describing barriers to adherence. Strategies commonly used include encouraging use of an alarm and a treatment supporter, linking ART taking to daily routines, and disclosure of HIV status. The first session is given on the day of receiving viral load results, with two subsequent sessions scheduled on a monthly basis. Referrals may be made to local support groups or organisations for social or economic support, general psychological support or to an HIV clinician. The HIV operational strategy recommends that all patients living with HIV and registered at facility should be screened for common mental disorders (CMD) annually. Patients with high viral load or those initiating ART should be screened for CMD at their appointment (45). Patients exhibiting symptoms of common mental disorders or psychological distress should be managed with counselling interventions and are usually referred to the outpatient's department to be assessed by a Psychiatric nurse. If they require further treatment, they will be seen by a psychiatrist. Patients can also be referred to community-based organization to receive psychosocial services (45). Usual care for depression is enhanced in three ways: 1) The study team will train all health service providers in the study sites on psychological and antidepressant management of depression using the WHO Mental Health Gap intervention guide (mhGAP) (46); 2) we will provide a letter for each participant communicating the patients PHQ-9 score and probable depression to their HIV-care provider; and 3) we will provide those in the EUC condition with access to Stepped Care-AD upon completion of their 12-month follow-up visit.

Outcomes

Primary Outcome

Viral suppression at 12-months post-randomisation follow-up (defined as <1000 copies/mL), measured through blood (plasma). This measure will be taken from the medical record if viral load was collected 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 randomisation measured as the total score on the Patient Health Questionnaire (PHQ-9) (6).
2. Adherence to ART medication at 4-, 8-, and 12-months post randomisation assessed as the proportion of the sample achieving at least 90% adherence in the past month assessed through pharmacy refill (47).
3. Self-reported adherence to ART medication at 4-, 8-, and 12-months post randomisation assessed as the frequency of adherence in the past 30 days measured using a score derived from a three-item questionnaire adapted from Wilson et al. (2015)(48).
4. Viral load copies/mL at 12-months post-randomisation follow-up measured as mean log Viral Load.

Tertiary Outcomes

The total costs of the health care services used by each study participant will be calculated using service use information collected from hospital records and from participant self-report (via a modified version of the Client Services Receipt Inventory suitable for use in sub-Saharan Africa (38)) at 4-, 8-, and 12-month follow-up and with unit costs identified and calculated using locally available data. Detailed information on the use of Stepped Care-AD and EUC will be collected from therapist records. Quality of life at 4, 8 and 12 months is measured

using EQ-5D-3L (32). Quality-adjusted life years will be calculated using Zimbabwe-specific health states (37).

Data Collection and Management

Trial data is collected and stored in REDCap, a data management tool designed for collection and protection of patient health information. The REDCap database is hosted and routinely audited at Massachusetts General Hospital (MGH), with access restricted via user roles. Data extracts are sent to the study statisticians, via secure file transfer. To ensure accuracy of collected data, MGH staff generate weekly error reports. These error reports are then sent to staff in Zimbabwe, who correct any discrepancies and document changes made to the database.

Strategies to Improve Participant Retention

Procedures to maximise participant retention include reimbursing participants for attending study visits (equal amount in both arms), sending text message reminders before scheduled appointments and collection of locator information (e.g., contact information of two significant others with whom the participant is in regular contact). 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. Where participants are unable to travel to the clinic to complete follow up assessments (e.g. because of COVID-19 lockdown travel restriction), participants will be offered phone assessments. Where participants can not be reached by phone, a home visit may be conducted.

Ethics

All study procedures were reviewed and approved by ethics committees at King's College London (RESCM-17/18-5580), Massachusetts General Hospital (IRB00012706), and the Medical Research Council of Zimbabwe (MRCZ/A/2390). Serious adverse events (SAEs)

will be reported to research ethics committees at King's College London, MGH, and the Medical Research Council of Zimbabwe within 72 hours.

Confidentiality

Participants are given a study-specific identification number at screening that is used on all forms and data collection instruments, excluding the consent form. Participants are referred to only by their identification number during eligibility and supervision meetings. A file that links participant names to identification numbers is stored in a locked file at the University of Zimbabwe.

Blinding

To reduce bias and maximise the validity of the findings, the Independent Assessor (IA) for the primary and secondary outcomes, and the lead study statistician, are blinded to randomisation condition. To ensure blinding, the IA will explain their role to participants and ask that they do not give the IA information about the treatment they received. The lead study statistician will not attend meetings where randomisation or clinical issues are discussed, and their access in REDCap is restricted so that they cannot view any data or report that may unblind them. A second statistician, who will conduct the analyses and will review data for thoroughness and completeness, will not be blinded. This trial does not have procedures for unblinding IAs or the lead study statistician. If the IA is concerned about the safety of a participant, they will communicate the concern to study staff, who will contact the clinical supervisor.

Data Safety and Monitoring Board (DSMB)

A DSMB, consisting of members with experience in clinical trials for mental disorders, biostatistics, HIV in African settings, and human subject protection issues will function independent of the sponsor and monitor safety of study participants and integrity of data. The

DSMB will meet annually and receive safety information in an unblinded manner. Expedited review by the DSMB will occur for all serious adverse events (SAE) as defined as any fatal, immediately life-threatening, or substantially disabling event; event requiring or prolonging inpatient hospitalisation, or any congenital anomaly.

Statistical Methods

Sample Size

Using two-sided Fisher's exact test, $\alpha = 0.05$ and 20% attrition, 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. Pilot data showed a larger difference between arms (50% in the EUC arm vs. 75% in the intervention arm) (23), suggesting this should be a conservative sample size estimate.

Statistical Methods for Primary and Secondary Outcomes

Baseline and outcome variables will be summarised using appropriate statistics; no baseline statistical comparisons will be made. The main analysis will follow intention to treat principles , reporting appropriate 95% confidence intervals and use a 5% significance level. All models will include a site stratification variable. In the mixed models we will have random intercepts at the participant level, and random slopes if warranted (assessed via likelihood ratio test).

Twelve-month primary outcome viral load will be coded as suppressed (<1000 copies/mL) vs not suppressed (>=1000 copies/mL). Where these data are missing, the individual has died, and medical or death records indicate death due to high viral load/death was AIDS related, they will be coded as not suppressed, otherwise the outcome will be left missing. Suppressed/not suppressed will be the dependent variable in a logistic regression model

estimating the TENDAI vs EUC odds ratio (OR), with trial arm as the independent variable. The mean difference in PHQ-9 depression and self-report adherence will each be estimated using a linear mixed effects model with the 4-, 8- and 12-month measures as dependent variables, with the baseline measure of the outcome, time, and trial arm by time interaction terms as independent variables. The OR at 4, 8 and 12 months for ≥90% adherence vs＜90% adherence by pharmacy refill in the past 30 days will be estimated using a logistic mixed effects model with the 4, 8 and 12-month measures as dependent variables, and independent variables as described for PHQ-9 and self-report adherence. The mean difference in log copies/mL of viral load at 12 months will be estimated using a linear regression model with log viral load at 12 months as the dependent variable, trial arm and baseline log viral load as independent variables.

A "per protocol" analysis for the primary viral load outcome only will exclude participants not completing at least four TENDAI sessions, and anyone found to be ineligible post randomisation. No interim or formal powered subgroup analyses are planned, however, we will explore moderation by gender for viral suppression, self-report adherence and depression outcomes by adding a sex by trial arm (by time, where appropriate) interaction term to the final outcome analysis models. Additional exploratory mediation analysis (e.g., to examine changes in both depression and adherence as mediators of treatment related changes in viral load) is planned, but will not be reported on in the main paper. Missing baseline measures will be imputed using simple mean imputation (49). Missing repeatedly measured outcome data will be handled using mixed models/maximum likelihood methods, including baseline variables predicting missing outcome data. If there is more than 10% missing primary outcome data and post-randomisation variables (completion of therapy in the TENDAI arm only and ART

adherence at 12 months) predict whether these data are missing, we will consider multiple imputation (MI) (50).

Cost-effectiveness results will be reported following CHEERS guidelines (51). Economic evaluations can be used to inform healthcare decision makers on the total budget needed to treat people with a particular disease or condition; it is only the mean cost that allows for this calculation to be made. Thus, it is the arithmetic mean cost that is the relevant summary statistic in pragmatic trials with economic evaluations and the mean average total cost in each randomised group will be calculated and compared between the two groups using standard t-tests, despite the likely skewed nature of the data (52). 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 (53). The primary cost-effectiveness will consider costs together with the dichotomous primary outcome measure (viral suppression <1000 copies/mL), generating information on the incremental cost per successful case (in the form of an incremental cost-effectiveness ratio) and the probability that the TENDAI 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 the TENDAI intervention compared to enhanced usual care via incremental cost-effectiveness ratios. Analyses will be adjusted for costs and outcomes. Sensitivity analyses will be carried out to test the robustness of costing assumptions to variation.

Dissemination

Dissemination of findings will involve three primary papers describing the study outcomes, as well as submitting to lead workshops on the treatment approach at relevant national

meetings and conferences. Additionally, data will be available to external parties after publication of the outcome papers via PI-approved application. Data will be stored indefinitely.

Discussion

In Zimbabwe, both HIV and co-morbid depression are common, yet, as in other low-resource settings with high HIV burden, there is a lack of evidence on interventions to improve both ART adherence and depression (54). Due to resource limitations, interventions that allow for task-shifting and administration by community health workers are particularly well-placed to be effective and sustainable. Our treatment, Stepped Care-AD, blends active ingredients of treatment for depression with a culturally-adapted LifeSteps intervention to enhance adherence to ART (23, 40). If successful, the Stepped Care-AD intervention represents a useful model for policy and for further research. As the primary outcome of the trial is viral suppression, its implementation in Zimbabwe and other low-resource settings may further the UNAIDS goal of ending the AIDS epidemic by 2030, through optimising viral suppression (55). Results gathered in a Zimbabwean context may be leveraged for testing and implementation of similar task-shifted stepped care interventions in other Sub-Saharan African settings.

Trial Status

This trial began recruitment and enrolment on 2nd July 2019.

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Figure Legend

Figure 1. Flow of Participants through TENDAI Study.
Figure 2. Stepped Care-AD Intervention Flow Diagram.

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Figure 1: Participant Flow

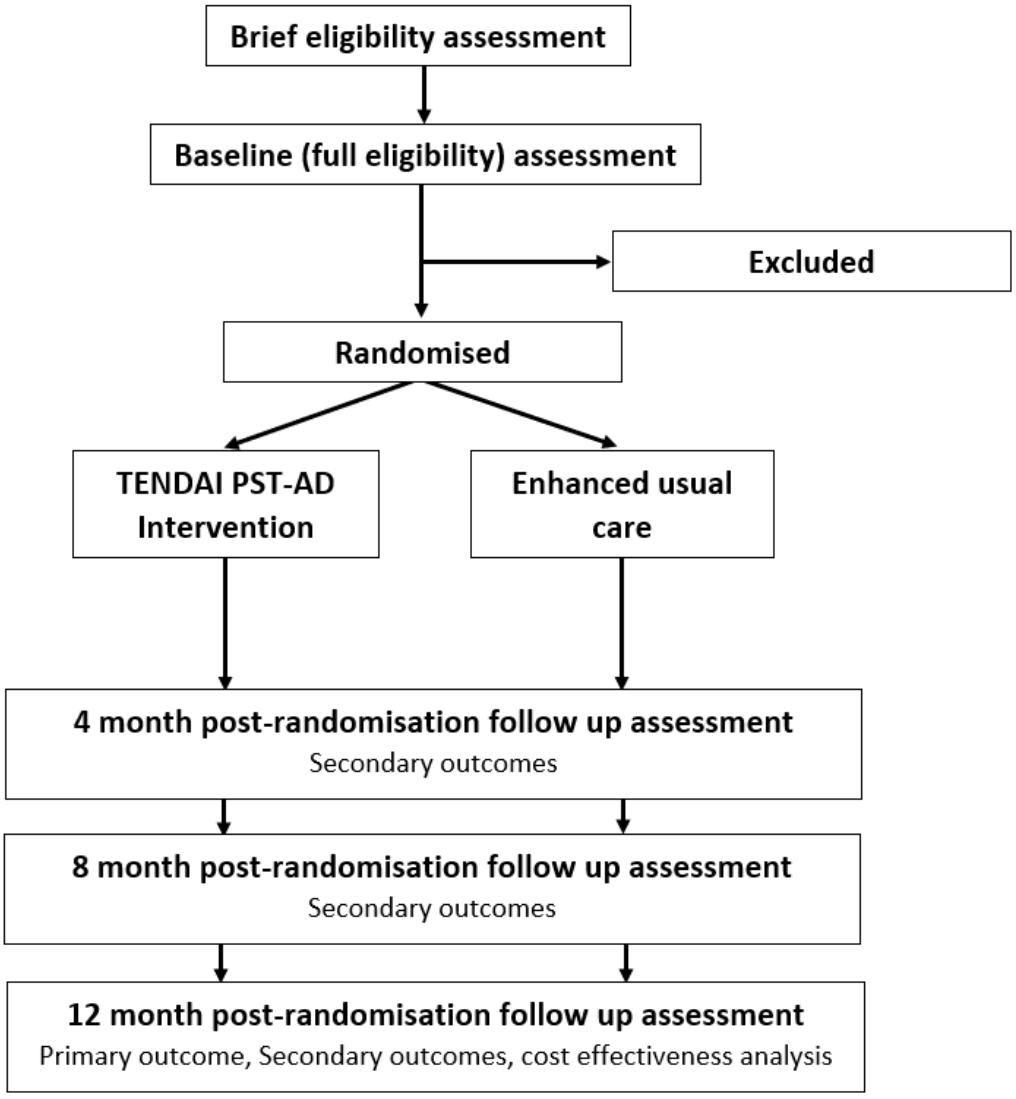
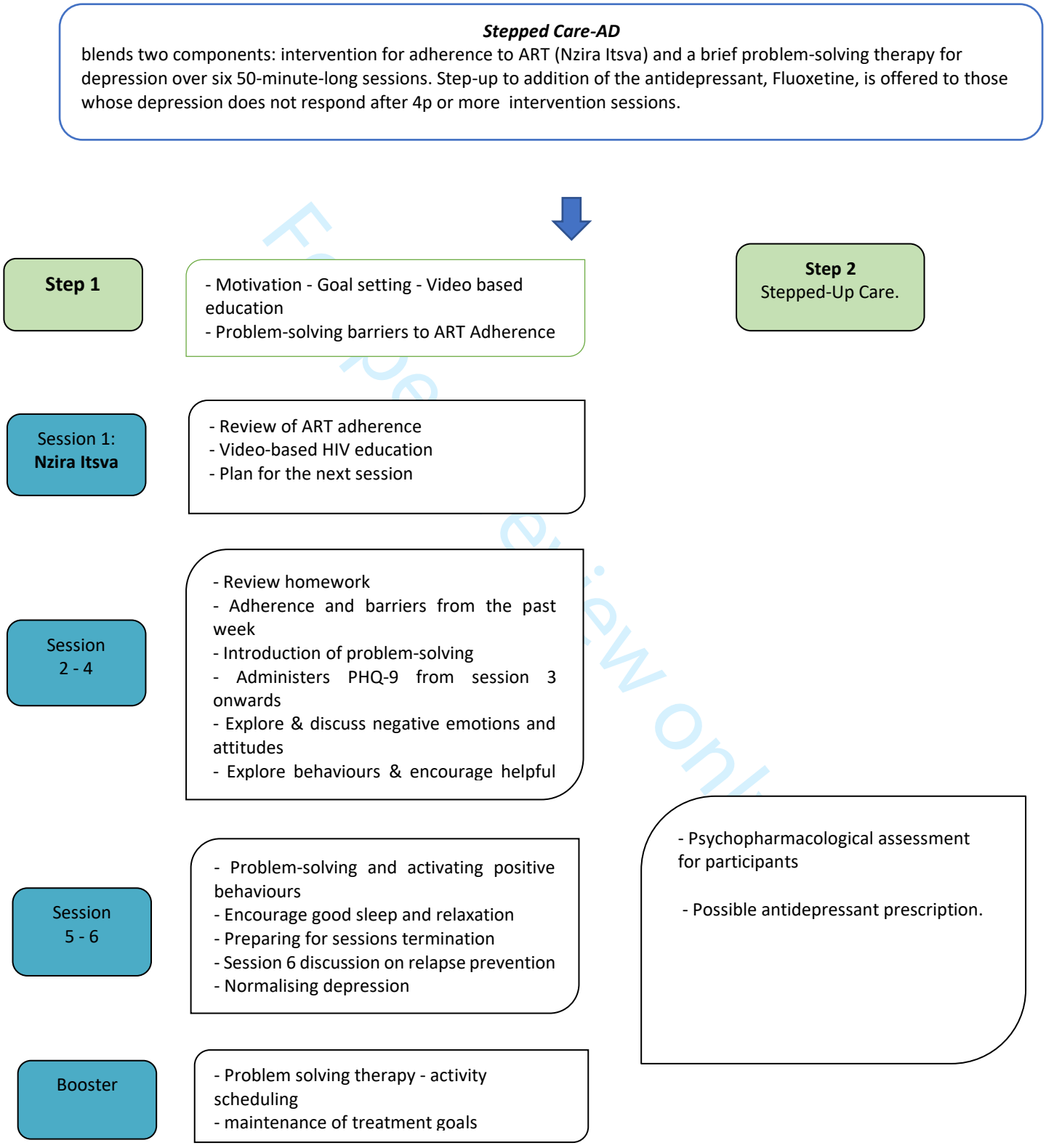


Figure 2: Stepped Care-AD Flow



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11, 19
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8, 20

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 12-13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13-14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12, 14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 6
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Task-sharing with lay counsellors to deliver a stepped care intervention to improve depression, antiretroviral therapy adherence, and viral suppression in people living with HIV: study protocol for the TENDAI randomised controlled trial.

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Mental health

Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Depression & mood disorders < PSYCHIATRY, HEALTH ECONOMICS, MENTAL HEALTH, PUBLIC HEALTH

Task-sharing with lay counsellors to deliver a stepped care intervention to improve depression, antiretroviral therapy adherence, and viral suppression in people living with HIV: study protocol for the TENDAI randomised controlled trial.

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Trial registration: ClinicalTrials.gov Identifier: NCT04018391

Abstract

Introduction: Non-adherence to antiretroviral therapy (ART) is the main cause of viral non-suppression and its risk is increased by depression. In countries with high burden of HIV there is a lack of trained professionals to deliver depression treatments. This paper describes the protocol for a 2-arm parallel group superiority 1:1 randomised controlled trial, to test the effectiveness and cost-effectiveness of the TENDAI stepped care task-shifted intervention for depression, ART non-adherence, and HIV viral suppression delivered by lay interventionists. Methods and Analysis: Two hundred and ninety people living with HIV (PLHIV) aged ≥18 years with probable depression (Patient Health Questionnaire =>10) and viral non-suppression (=> 1000 HIV copies per ml) are being recruited from HIV clinics in towns in Zimbabwe. The intervention group will receive a culturally adapted 6-session psychological treatment (PST-AD) including problem-solving therapy, positive activity scheduling, skills to cope with stress and poor sleep, and content to target barriers to non-adherence to ART. Participants whose score on the PHQ-9 remains >=10, and/or falls by less than 5-points, step up to a nurse-evaluation for possible antidepressant medication. The control group receives usual care for viral non-suppression, consisting of three sessions of adherence counselling from existing clinic staff, and enhanced usual care for depression in line with the WHO Mental Health Gap intervention guide. The primary outcome is viral suppression (<1000 HIV copies per ml) at 12 months post-randomisation. Ethics and Dissemination: The study and its tools were approved by MRCZ/A/2390 in Zimbabwe and RESCM-18/19-5580 in the United Kingdom. Study findings will be shared through the community advisory group, conferences, and open access publications.

Strengths and Limitations:

Strengths:

- The first randomised controlled trial in a low-income country to test an intervention to improve adherence to antiretroviral therapy (primary outcome) and depression (as a secondary outcome) in people living with HIV.

- Culturally adapted and culturally appropriate intervention to address barriers to adherence to antiretroviral therapy and to treat depression, based on extensive preliminary work.
- Assessment of the cost-effectiveness of the TENDAI stepped care task-shifted intervention
- Stepped care intervention is delivered through task-shifting to non-specialist staff, allowing for future scale up.

Limitation:

- Limited scope to assess implementation science questions given the individually randomised design.

Introduction

Over 27% of people in sub-Saharan Africa currently receiving antiretroviral therapy (ART) are non-adherent (1), and non-adherence to ART is the main cause of viral non-suppression (2). Achieving and maintain viral suppression is not only an effective HIV treatment strategy but also an effective HIV prevention approach, preventing transmission of the virus to sexual partners, and from mother to child (3, 4). Depression is among the strongest correlates of non-adherence and affects over 15% of PLHIV attending HIV out-patient clinics in sub-Saharan Africa (1, 5, 6). Depression is linked to non-adherence through the reduced motivation and forgetting to take ART (7), through impaired problem-solving ability (8), and may interfere with uptake of existing adherence support programs as part of clinical care (9, 10). Depression may also impact adherence through its association with structural factors, such as poverty, and interpersonal difficulties which impede access to HIV medication (7, 10, 11). Non-adherence to ART may also precede and increase risk of depression (12). Evidence-based interventions for depression include psychological interventions based on cognitive behavioural approaches, and antidepressant medication (13)

Countries with high burden of HIV, such as Zimbabwe, have a dearth of trained mental health professionals. Given the public health importance of viral suppression (14), and the strong association with depression, adherence interventions must address comorbid psychological factors and be able to be delivered through task-shifting to non-specialists (15). Systematic reviews of mental health interventions in PLHIV in low resource settings have

been unable to report effects on HIV outcomes as, to date, these have not been studied (16, 17).

The most promising evidence for the effectiveness and utility of integrated treatments for depression and ART adherence for PLHIV has come from the development of Cognitive Behavioural Therapy for Adherence and Depression (CBT-AD) in the United States (18, 19). CBT-AD, which includes the "Life Steps" intervention for addressing barriers to medication adherence, has been shown to improve rates of ART adherence, and to reduce depression severity among men in the US (20 , 21). In contrast, interventions for PLWH with depression and poor adherence which *only* target mood have not been found to improve viral suppression (22). Recent reports, including from our team in Zimbabwe, support the acceptability and feasibility of culturally-adapted cognitive behavioural interventions for low resource settings (23-25). However, there have yet to be any definitive RCTs from low resource settings focused on treatment of depression and ART adherence to improve viral suppression (26). Thirteen percent of the adult population in Zimbabwe is living with HIV, with 22% of those virally non-suppressed (22). The objective of this trial is to test the effectiveness and cost-effectiveness of the TENDAI stepped care psychological intervention for adherence to ART and depression, (Stepped Care-AD), compared to enhanced usual care, for PLHIV in Zimbabwe with viral non-suppression and depression. TENDAI is derived from principles of problem-solving and psychoeducation for depression and adherence, and motivational interviewing.

Methods and Analysis

Study Design and Setting

The study is a two-arm parallel group superiority 1:1 randomised effectiveness trial (n=290). PLHIV receive care according to the standard national guidelines (27). Viral load is monitored every 12 months, with more frequent screening every 3 months for those who are

virally non-suppressed. Participants are being recruited from two sites in Zimbabwe providing HIV services for those initiated on ART. These are the Marondera Provincial Hospital, and Chitungwiza Central Hospital, along with satellite clinics for each hospital. Marondera is the capital of Mashonaland East province, situated in the north east of Zimbabwe. The town and its surrounding district have a total population of approximately 224,000 (28). Chitungwiza is an urban town, divided into five townships, with a total population of approximately 391,000 (29). Taken together, both sites combined have approximately 25,000 adults registered as receiving ART.

Patient and Public Involvement

No patient involvement in the design of the study. Results will be disseminated to study participants and community members via local advisory groups.

Eligibility Criteria

Inclusion criteria: 1) HIV positive and initiated on ART for at least 6 months; 2) clinically significant depression symptoms (operationalised as a score of 10 or more on the locally validated Patient Health Questionnaire (PHQ-9) which has been validated for adults in a primary care population with high HIV prevalence in Zimbabwe (6)); 3) virally non-suppressed in the past 2 months (viral load >/= 1000 copies/mL); 4) able to provide informed consent ; and 5) if prescribed anti-depressants, have been on a stable anti-depressant regimen for at least 2 months. Exclusion criteria: 1) unwilling or unable to provide informed consent; 2) major untreated or undertreated mental illness (e.g. untreated psychosis or mania, actively suicidal assessed using the MINI and P4 suicide screener), major or advanced physical disease (assessed using clinic records) or severe cognitive impairment (assessed using the International HIV dementia scale) which would interfere with engagement in Stepped Care-AD; 3) have received a course of problem solving therapy or cognitive-behavioural psychological therapy for depression; or 4) <18 years old.

Study Procedures

Recruitment and Informed Consent

See Figure 1 for study flow. Research Assistants (RAs) in the ART clinic approach patients identified by clinic staff as having a detectable viral load (>1000 copies/mL) in the past 2 months or at high risk of viral non-suppression, e.g., self-reported poor adherence. Potentially eligible individuals will complete a brief screen for inclusion and exclusion criteria. Those meeting initial screening eligibility criteria are invited to complete informed consent procedures and the full baseline assessment. Informed consent will include consent to access participants' medical records, and for telephone calls and home visits if needed for follow-up. Capacity to provide consent is assessed by a licensed psychiatrist (WM) for any participant indicating consent but suspected of being unable to fully understand and/or retain information provided.

Baseline

A trained RA collects data by face-to-face interview including: demographics, measures of socio-economic position (employment status, educational history, and ownership of household assets) (30, 31), depression using the Patient Health Questionnaire (PHQ-9) (6), anxiety using the Hospital Anxiety and Depression Scale (32) quality of life using The EQ-5D-3L (33), use of alcohol and substances (34, 35), cognitive impairment using the International HIV Dementia Scale (36), psychiatric diagnosis using the MINI International Neuropsychiatric Interview (37), use of health services in the last 4 months using a modified version of the Client Services Receipt Inventory (31) and several additional exploratory measures. Current ART regimen and recent CD4 test results are taken directly from participants medical records.

Viral load in the past 60 days is ascertained from the participants medical records, or, for those who have not been tested in the past two months, by testing plasma.

Eligibility

The study team, including a clinical psychologist or psychiatrist, will meet weekly via teleconference to discuss each baseline assessment and confirm that participants meet eligibility criteria.

Randomisation

Approximately 2 weeks after the baseline assessment, eligible participants return for a randomisation visit and are randomly assigned to Stepped Care-AD or enhanced usual care (EUC). Randomisation is determined by a computer-generated chart and is conducted via the REDCap randomisation module by the Zimbabwe site Programme Manager.

Follow-Up Assessments

In addition to baseline, there are 3 major study assessments: 4-, 8-, and 12-months post-randomisation. An Independent Assessor (IA) who is blind to study condition will administer the PHQ-9, EQ-5D-3L, and self-report medication adherence measures only. RAs will collect all other self-report data including use of alcohol and substances (34, 35), Hospital Anxiety and Depression Scale for Anxiety (32), quality of life (33), and use of other health care services (38). 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. Participants without a viral load test in the past 30 days are invited to undergo venepuncture for viral load testing, which is in addition to the venepuncture for ART detection.

Interventions

Active Intervention Arm: Task-sharing Stepped Care Intervention for Adherence and Depression (TENDAI Stepped Care-AD).

As shown in Figure 2, all participants in the TENDAI arm receive six 50-minute sessions of a culturally adapted intervention for depression and non-adherence to ART delivered weekly, followed by one booster session six weeks later. The intervention is based

on cognitive behavioural principles and includes problem-solving therapy, positive activity scheduling, skills to cope with stress and poor sleep, and content to target barriers to non-adherence to ART. Training of interventionists emphasises common elements of effective psychological interventions including empathy, active listening, and creating realistic hope (39). The training is conducted by the principal investigators and other clinical psychologists with expertise in the intervention. Refresher trainings and ongoing supervision will be conducted throughout the study.

A) Adherence to antiretroviral therapy. Session 1 comprises a locally adapted version of the Lifesteps adherence intervention called *Nzira Itsva* (18, 40). This includes motivation, goal setting, video-based education and problem solving. Motivational interviewing is used to identify the participants' life goals and to tie adherence to achieving these goals. Education about on time adherence is provided using an animated video in the Shona language. Barriers to adherence are assessed through a culturally adapted checklist. During each of the subsequent sessions 2-6 targeting depression, 5- to 10-minute adherence boosters are included to review adherence to ART and the participants' experience with strategies to overcome barriers to adherence.

B) Psychological intervention for depression. Sessions 2 and 3 focus on psychoeducation about depression and problem-solving therapy (PST) (41), incorporating storytelling and illustrations, and training in problem-solving. A goal for each session is to identify a defined specific problem to work on, to collaboratively agree a solution to work on and to schedule homework. An intervention based on PST has been shown to be acceptable and effective for depression in Zimbabwe (42, 43). In Session 4 participants are encouraged to choose and schedule at least four adaptive activities in which to engage: an activity that promotes a sense of achievement, a physical activity, a pleasurable activity, and a social activity. Homework is mutually agreed as part of every session, to test out participants'

implementation of solutions to problems, and of positive activities. Thorough review of homework is done at each session, including barriers to doing homework. Skills to promote good sleep and relaxation are taught in Sessions 5 and 6. A relapse prevention plan is developed in session 6 including triggers for relapse of depression, warning signs, coping strategies and self-care activities. Fidelity of the intervention will be assessed through rating 10% of audio-recorded sessions for adherence to the intervention protocol and for therapist competence (44).

C) Booster session. About six weeks after the sixth session, participants are invited to a 50-minute booster session. This includes a review of depressive symptoms, and of adherence to HIV treatment and, where appropriate, adherence to antidepressant medication. The session includes ongoing positive activity scheduling to promote recovery from depressive symptoms.

D) Stepped up care. Participants with persistent depression (depression score continuing above cut-off (PHQ-9 >=10) or if they have less than a 5-point improvement in PHQ-9 score) after at least 4 sessions receive step up to a nurse-evaluation for antidepressant medication. The antidepressant Fluoxetine is offered for those with confirmed depression.

Control Arm: Enhanced Usual Care (EUC)

All participants in the control arm receive Enhanced Usual Care (EUC) comprising usual care for viral non-suppression, and enhanced usual care for depression in line with the WHO Mental Health Gap intervention guide. Usual care for those with viral non-suppression includes three sessions of adherence counselling provided by an adherence counsellor, nurse, or NGO support worker based at the clinic. These sessions include establishing the participants knowledge about HIV and ART, providing information about use of ART, encouraging adherence, and describing barriers to adherence. Strategies commonly used include encouraging use of an alarm and a treatment supporter, linking ART taking to daily

routines, and disclosure of HIV status. The first session is given on the day of receiving viral load results, with two subsequent sessions scheduled on a monthly basis. Referrals may be made to local support groups or organisations for social or economic support, general psychological support or to an HIV clinician. The HIV operational strategy recommends that all patients living with HIV and registered at facility should be screened for common mental disorders (CMD) annually. Patients with high viral load or those initiating ART should be screened for CMD at their appointment (45). Patients exhibiting symptoms of common mental disorders or psychological distress should be managed with counselling interventions and are usually referred to the outpatient's department to be assessed by a Psychiatric nurse. If they require further treatment, they will be seen by a psychiatrist. Patients can also be referred to community-based organization to receive psychosocial services (45). Usual care for depression is enhanced in three ways: 1) The study team will train all health service providers in the study sites on psychological and antidepressant management of depression using the WHO Mental Health Gap intervention guide (mhGAP) (46); 2) we will provide a letter for each participant communicating the patients PHQ-9 score and probable depression to their HIV-care provider; and 3) we will provide those in the EUC condition with access to Stepped Care-AD upon completion of their 12-month follow-up visit.

Outcomes

Primary Outcome

Viral suppression at 12-months post-randomisation follow-up (defined as <1000 copies/mL), measured through blood (plasma). This measure will be taken from the medical record if viral load was collected 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-randomisation measured as the total score on the Patient Health Questionnaire (PHQ-9) (6).
2. Adherence to ART medication at 4-, 8-, and 12-months post randomisation assessed as the proportion of the sample achieving at least 90% adherence in the past month assessed through pharmacy refill (47).
3. Self-reported adherence to ART medication at 4-, 8-, and 12-months post randomisation assessed as the frequency of adherence in the past 30 days measured using a score derived from a three-item questionnaire adapted from Wilson et al. (2015)(48).
4. Viral load copies/mL at 12-months post-randomisation follow-up measured as mean log Viral Load.

Tertiary Outcomes

The total costs of the health care services used by each study participant will be calculated using service use information collected from hospital records and from participant self-report (via a modified version of the Client Services Receipt Inventory suitable for use in sub-Saharan Africa (38)) at 4-, 8-, and 12-month follow-up and with unit costs identified and calculated using locally available data. Detailed information on the use of Stepped Care-AD and EUC will be collected from therapist records. Quality of life at 4, 8 and 12 months is measured using EQ-5D-3L (33). Quality-adjusted life years will be calculated using Zimbabwe-specific health states (49).

Data Collection and Management

Trial data is collected and stored in REDCap, a data management tool designed for collection and protection of patient health information. The REDCap database is hosted and routinely audited at Massachusetts General Hospital (MGH), with access restricted via user roles. Data extracts are sent to the study statisticians, via secure file transfer. To ensure

accuracy of collected data, MGH staff generate weekly error reports. These error reports are then sent to staff in Zimbabwe, who correct any discrepancies and document changes made to the database.

Strategies to Improve Participant Retention

Procedures to maximise participant retention include sending text message reminders before scheduled appointments and collection of locator information (e.g., contact information of two significant others with whom the participant is in regular contact). Participants are also provided with refreshments at study visits and reimbursed transport costs. Although those in the EUC arm have fewer scheduled clinical sessions, the same total amount ($46) will be provided to participants attending all clinical sessions and research assessments in both arms. 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. Where participants are unable to travel to the clinic to complete follow up assessments (e.g. because of COVID-19 lockdown travel restriction), participants will be offered phone assessments. Where participants can not be reached by phone, a home visit may be conducted.

Confidentiality

Participants are given a study-specific identification number at screening that is used on all forms and data collection instruments, excluding the consent form. Participants are referred to only by their identification number during eligibility and supervision meetings. A file that links participant names to identification numbers is stored in a locked file at the University of Zimbabwe.

Blinding

To reduce bias and maximise the validity of the findings, the Independent Assessor (IA) for the primary and secondary outcomes, and the lead study statistician, are blinded to randomisation condition. To ensure blinding, the IA will explain their role to participants and

ask that they do not give the IA information about the treatment they received. The lead study statistician will not attend meetings where randomisation or clinical issues are discussed, and their access in REDCap is restricted so that they cannot view any data or report that may unblind them. A second statistician, who will conduct the analyses and will review data for thoroughness and completeness, will not be blinded. This trial does not have procedures for unblinding IAs or the lead study statistician. If the IA is concerned about the safety of a participant, they will communicate the concern to study staff, who will contact the clinical supervisor.

Data Safety and Monitoring Board (DSMB)

A DSMB, consisting of members with experience in clinical trials for mental disorders, biostatistics, HIV in African settings, and human subject protection issues will function independent of the sponsor and monitor safety of study participants and integrity of data. The DSMB will meet annually and receive safety information in an unblinded manner. Expedited review by the DSMB will occur for all serious adverse events (SAE) as defined as any fatal, immediately life-threatening, or substantially disabling event; event requiring or prolonging inpatient hospitalisation, or any congenital anomaly.

Statistical Methods

Sample Size

Using two-sided Fisher's exact test, $\alpha = 0.05$ and 20% attrition, 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. Pilot data showed a larger difference between arms (50% in the EUC arm vs. 75% in the intervention arm) (24), suggesting this should be a conservative sample size estimate.

Statistical Methods for Primary and Secondary Outcomes

Baseline and outcome variables will be summarised using appropriate statistics; no baseline statistical comparisons will be made. The main analysis will follow intention to treat principles, reporting appropriate 95% confidence intervals and use a 5% significance level. All models will include a site stratification variable. In the mixed models we will have random intercepts at the participant level, and random slopes if warranted (assessed via likelihood ratio test).

Twelve-month primary outcome viral load will be coded as suppressed (<1000 copies/mL) vs not suppressed (>=1000 copies/mL). If these data are missing and we have no further information, they will be left as missing. If we do have information from medical or death records that the individual died from high viral load or AIDS related reasons, we will code them as not being virally suppressed. . Suppressed/not suppressed will be the dependent variable in a logistic regression model estimating the TENDAI vs EUC odds ratio (OR), with trial arm as the independent variable. The mean difference in PHQ-9 depression and self-report adherence will each be estimated using a linear mixed effects model with the 4-, 8- and 12-month measures as dependent variables, with the baseline measure of the outcome, time, and trial arm by time interaction terms as independent variables. The OR at 4, 8 and 12 months for ≥90% adherence vs＜90% adherence by pharmacy refill in the past 30 days will be estimated using a logistic mixed effects model with the 4, 8 and 12-month measures as dependent variables, and independent variables as described for PHQ-9 and self-report adherence. The mean difference in log copies/mL of viral load at 12 months will be estimated using a linear regression model with log viral load at 12 months as the dependent variable, trial arm and baseline log viral load as independent variables. In line with other recent and similar trials in HIV and methodology literature (50-56), we do not plan to undertake secondary outcome adjustment for multiple comparisons. Rather we will focus on our single pre-specified primary outcome to assess effectiveness and take a “precise

interpretation"/separate hypotheses approach for the secondary outcomes in combination with appropriate reporting of effect sizes and confidence intervals to support transparent interpretation (52, 56).

A "per protocol" analysis for the primary viral load outcome only will exclude participants not completing at least four TENDAI sessions, and anyone found to be ineligible post randomisation. No interim or formal powered subgroup analyses are planned, however, we will explore moderation by gender for viral suppression, self-report adherence and depression outcomes by adding a sex by trial arm (by time, where appropriate) interaction term to the final outcome analysis models. Additional exploratory mediation analysis (e.g., to examine changes in both depression and adherence as mediators of treatment related changes in viral load) is planned, but will not be reported on in the main paper. This analysis should help elucidate whether intervention effects were due to improving depression or more directly by changing adherence. Missing baseline measures will be imputed using simple mean imputation (57). Missing repeatedly measured outcome data will be handled using mixed models/maximum likelihood methods, including baseline variables predicting missing outcome data. If there is more than 10% missing primary outcome data and post-randomisation variables (completion of therapy in the TENDAI arm only and ART adherence at 12 months) predict whether these data are missing, we will consider multiple imputation (MI) (58).

Cost-effectiveness results will be reported following CHEERS guidelines (59). Economic evaluations can be used to inform healthcare decision makers on the total budget needed to treat people with a particular disease or condition; it is only the mean cost that allows for this calculation to be made. Thus, it is the arithmetic mean cost that is the relevant summary statistic in pragmatic trials with economic evaluations and the mean average total cost in each randomised group will be calculated and compared between the two groups using

standard t-tests, despite the likely skewed nature of the data (60). 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 (61). The primary cost-effectiveness will consider costs together with the dichotomous primary outcome measure (viral suppression <1000 copies/mL), generating information on the incremental cost per successful case (in the form of an incremental cost-effectiveness ratio) and the probability that the TENDAI 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 the TENDAI intervention compared to enhanced usual care via incremental cost-effectiveness ratios. Analyses will be adjusted for costs and outcomes. Sensitivity analyses will be carried out to test the robustness of costing assumptions to variation.

Discussion

In Zimbabwe, both HIV and co-morbid depression are common, yet, as in other low-resource settings with high HIV burden, there is a lack of evidence on interventions to improve both ART adherence and depression (62). Due to resource limitations, interventions that allow for task-shifting and administration by community health workers are particularly well-placed to be effective and sustainable. Our treatment, Stepped Care-AD, blends active ingredients of treatment for depression with a culturally-adapted LifeSteps intervention to enhance adherence to ART (24, 40). If successful, the Stepped Care-AD intervention represents a useful model for policy and for further research. As the primary outcome of the trial is viral suppression, its implementation in Zimbabwe and other low-resource settings may further the UNAIDS goal of ending the AIDS epidemic by 2030, through optimising viral suppression (63). Results gathered in a Zimbabwean context may be leveraged for

testing and implementation of similar task-shifted stepped care interventions in other Sub-Saharan African settings.

Ethics and Dissemination

All study procedures were reviewed and approved by ethics committees at King's College London (RESCM-17/18-5580), Massachusetts General Hospital (IRB00012706), and the Medical Research Council of Zimbabwe (MRCZ/A/2390). Serious adverse events (SAEs) will be reported to research ethics committees at King's College London, MGH, and the Medical Research Council of Zimbabwe within 72 hours.

Dissemination of findings will involve three primary papers describing the study outcomes, as well as submitting to lead workshops on the treatment approach at relevant national meetings and conferences. Additionally, data will be available to external parties after publication of the outcome papers via PI-approved application. Data will be stored indefinitely.

Trial Status

This trial began recruitment and enrolment on 2nd July 2019.

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Figure Legend

Figure 1. Flow of Participants through TENDAI Study.
Figure 2. Stepped Care-AD Intervention Flow Diagram.

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Date and Version: 10 June 2022, version 3.0
Competing Interests: The authors do not have any conflicts of interest to report.
Data Sharing: Trial data will be shared upon reasonable request.

Roles of Contributors

Melanie A Abas: Professor Abas is the King's College London PI for the trial and engaged in substantial writing of this manuscript and gaining funding for the study.
Walter Mangezi: Dr. Mangezi is the University of Zimbabwe PI for the trial and engaged in revision of this manuscript and gaining funding for the study.
Primrose Nyamayaro: Ms. Nyamayaro is the University of Zimbabwe Project Director for the trial and engaged in revision of this manuscript.
Rebecca Jopling: Ms. Jopling is the King's College London Project Director for the trial and engaged in substantial writing of this manuscript.
Tarisai Bere: Mrs. Bere is the University of Zimbabwe Clinical Supervisor for the trial and engaged in substantial writing of this manuscript.
Samantha M. McKetchnie: Mrs. McKetchnie is the trial Data Manager and engaged in substantial writing of this manuscript.
Kimberley Goldsmith: Dr. Goldsmith is the Trial Statistician and engaged in substantial writing of this manuscript and gaining funding for the study.
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Dixon Chibanda: Dr. Chibanda is a Co-Investigator on this trial and provided guidance around the development and execution of this manuscript and gaining funding for the study.
James Hakim: Professor. Hakim was a Co-Investigator on this trial. He assisted in gaining funding for the study and provided guidance around the development and execution of this manuscript up until his untimely death in 2020.
Steven A. Safren: Professor. Safren is a Co-Investigator on this trial and provided guidance around the development and execution of this manuscript and gaining funding for the study.
Conall O'Cleirigh: Dr. O'Cleirigh is the Massachusetts General Hospital PI for the trial and engaged in substantial writing of this manuscript and assisted in gaining funding for the study.
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Figure 1: Participant Flow

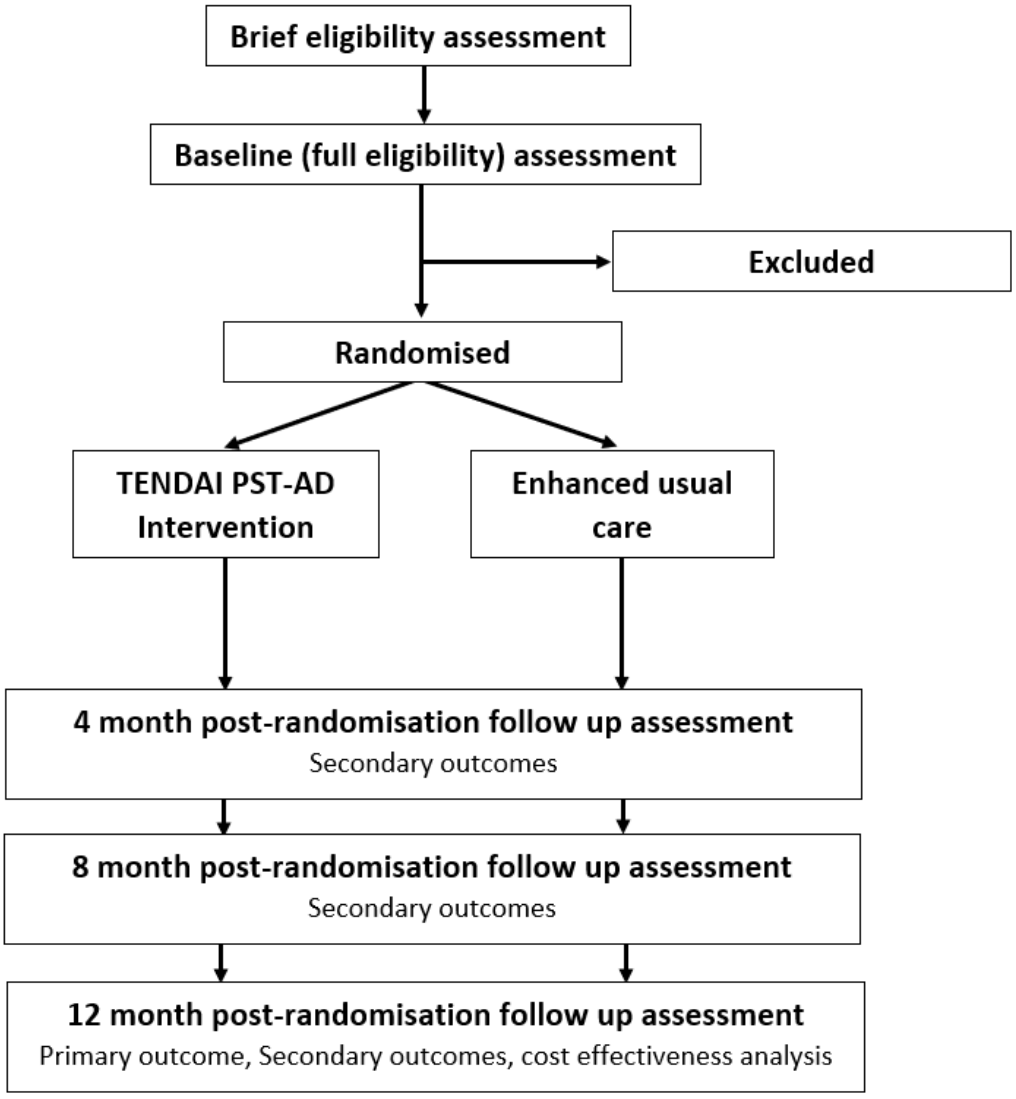
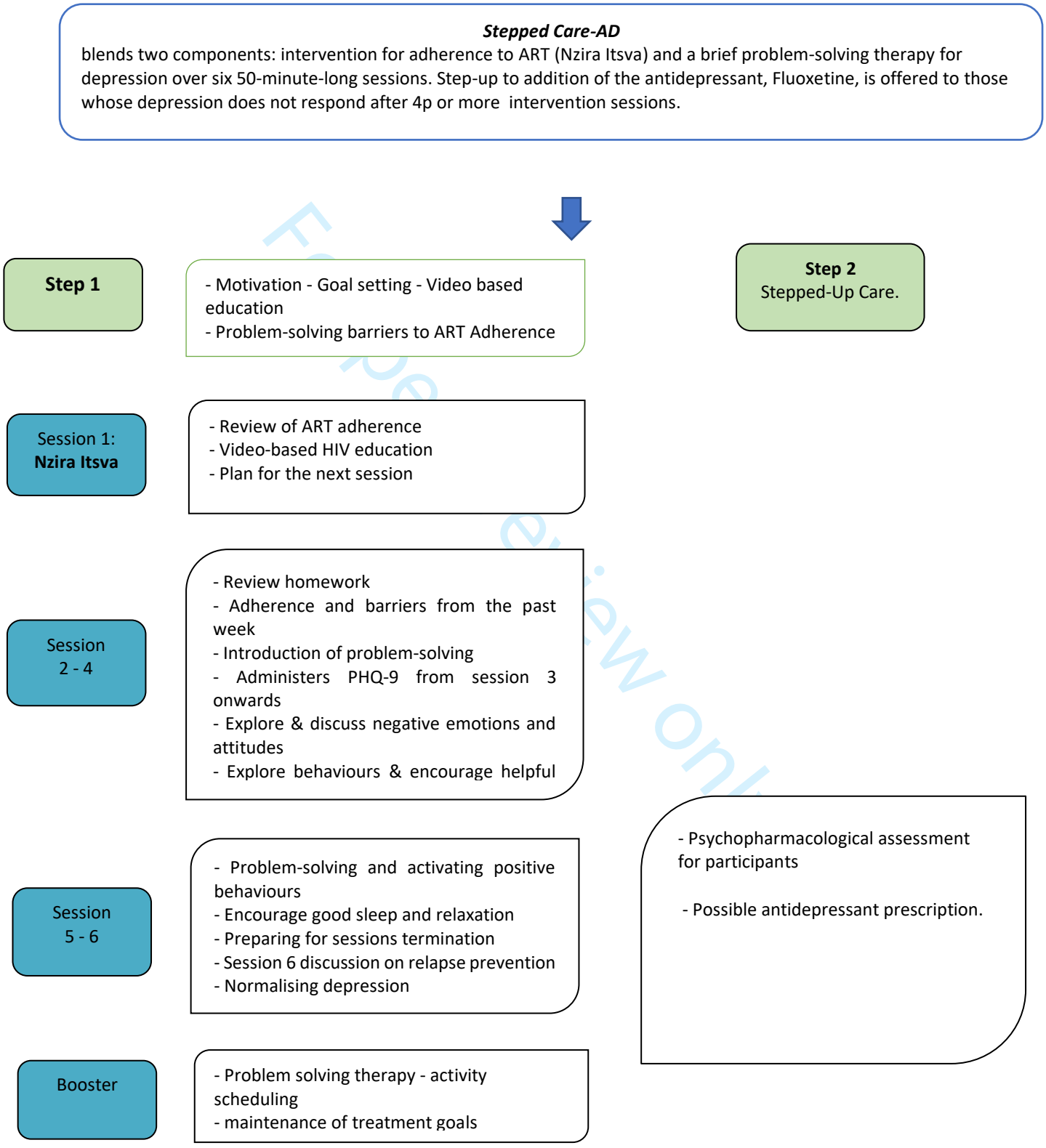


Figure 2: Stepped Care-AD Flow



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11, 19
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8, 20

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 12-13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13-14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12, 14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 6
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.