The TENDAI Steps Together Trial: Task Shifting to Treat Depression and HIV Medication Nonadherence in Low Resource Settings (TENDAI)

A randomised controlled trial of the effectiveness of the TENDAI intervention in a real-world setting

Statistical Analysis Plan
Version 2.0
22/08/2022

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Amendments to SAP after signoff of version 1.0

Note: V1.0 was not fully signed off by the TSC chair as there were TSC comments to incorporate, however, we have listed amendments to V1.0 regardless.

Date	SAP version	Protocol version and date	Reason for change
12/11/2020	V1.0	V7	Initial version
16/12/2020	V1.01	V9 14/07/2021	Changes outlined as below – not circulated as not completed, so started new version 1.02
23/03/2022	V1.02	TENDAI protocol Version 10.0 2022 (2)	Updates to status of trial personnel Some correction of typos, redundancies and minor clarifications throughout Addition of a second recruitment site, Sections 1.2, 1.4, 2.2, 3.1 COVID-19 measures have been added, Section 1.8.1, 5 Clarification of blinding status of senior statistician, Section 3.1 Clarify will fit two binary viral suppression models one without baseline viral load (providing marginal estimate), one with (providing conditional estimate), Section 3.1, 3.1.1 Add consideration of random slopes for mixed models, setting of undetectable viral loads, and clarification of presentation of results from logistic mixed and GEE models, Section 3.1.2 Clarify predictors in moderation models and that time will not be included for PHQ-9/will be average effect over course of follow-up, Section 3.1.3 Clarify adherence variable assessed to predict missing data is self-report adherence, Section 3.1.4.5 Clarify variables for imputation model and correct process for incorporating moderating variable in imputation model, Section 3.1.4.5 Clarify that per protocol analysis will only be done for primary outcome binary viral suppression, Section 3.1.4.7 Clarification and change to viral load assumption for deaths sensitivity analyses, Section 3.1.5.1 Addition of COVID-19-related data summaries and sensitivity analyses, Section 3.1.5.2 Software – update to Stata versions

			Replaced Appendix 1 Scoring with reference to up to date Codebook document with scoring
05/08/2022	V1.03	TENDAI protocol Version 11.0 Mar 2022	Comments added resolving queries to and by the team. Dates when COVID measures were added and a date for when the pandemic started to allow for analyses described in Section 3.1.5.2. Coding of occupations into an occupational class variable to be summarised at baseline, see Section 2.2
22/08/2022	V2.0	TENDAI protocol Version 11.0 Mar 2022	Create V2.0 signed by DSMB Chair

QUANTITATIVE ANALYSIS PLAN

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Contents

This document contains up to date statistical analysis plans (with version numbers and dates) including a quantitative analysis plan and a schedule of assessments and measures.

This SAP refers solely to the main analysis of the primary and secondary trial outcomes, i.e. the analysis to be performed in producing the main trial results paper. It mentions health economic, mediator, and other variables that have been measured, but does not describe these analyses associated with these variables. The health economic analysis will be described in a separate analysis plan. Any qualitative or mediation analysis plans will be dealt with in separate analysis plans.

1. Description of the trial

Problem Solving Therapy (PST), which is an evidence-based psychological and behavioural intervention for depression and an ingredient of CBT, has been previously been tested in a low-income country setting in treatment for depression, also for depression following gender-based violence and depression in post-conflict settings (Chibanda et al, Rahman et al). In Zimbabwe the study team has embedded PST into an intervention, stepped care for adherence (stepped care-AD). This form of PST combined with a culturally-adapted version of Life-Steps (a CBT and problem-solving methodology for improving adherence, viral suppression and depression) has been combined into a new intervention TENDAI (meaning 'thankful' in the Shona language). This has been tested in a feasibility trial in Zimbabwe (Nyamayaro et al, Abas et al). This trial aims to determine whether the TENDAI intervention is effective in a real-world setting.

The trial will recruit HIV positive, not virally suppressed patients who are able to provide informed consent, who have been taking anti-retroviral treatment (ART) for at least 6 months, who are clinically depressed and, where prescribed anti-depressants, have been on a stable regimen for at least 2 months. Those participants will be randomised 1:1 into enhanced usual care (EUC) or Stepped Care-AD (TENDAI). Please refer to the protocol v11.0 04 March 2022 for more detail.

1.1 Principal research objectives to be addressed

Primary objectives

To evaluate the effectiveness of the task-shifted stepped care-AD intervention on viral suppression compared with Enhanced Usual Care (EUC) at 12-months post-randomisation follow-up.

Secondary objectives

To investigate the effectiveness of the TENDAI intervention compared with Enhanced Usual Care (EUC):

1. on depression at 12 months post-randomisation (PHQ-9),
2. on adherence at 4, 8 and 12 months post-randomisation defined as the proportion achieving at least 90% adherence assessed through pharmacy refill,
3. on adherence at 4, 8 and 12 months post-randomisation through self-report,
4. on viral load (mean log viral load of viral copies per mL) at 12 months post-randomisation.

Tertiary objectives

1. To estimate the cost effectiveness of the TENDAI intervention on viral suppression and quality of life at 12-months (using the CSRI and EQ-5D-3L (Shona dialect version). This tertiary objective will be addressed in a separate Health Economic Analysis Plan.

Exploratory Objectives

Additionally, we intend to investigate mediation and moderation hypotheses.

Mediation: we intend to investigate whether: a) the effect of TENDAI on the depression and adherence outcomes are mediated by improvements in social support, Adherence Self-efficacy scale (ASES) or Problem Solving Skills subscale (PSSS), b) the effect of TENDAI on viral suppression is mediated by depression or adherence. For (b) we will initially explore each of self-report, pharmacy refill, and DBS measures of adherence as separate potential mediators, then also a composite measure of adherence using all three as indicators of an adherence latent variable. As this SAP refers only to the analysis for the main trial paper, we will not describe the mediation analysis further in this document.

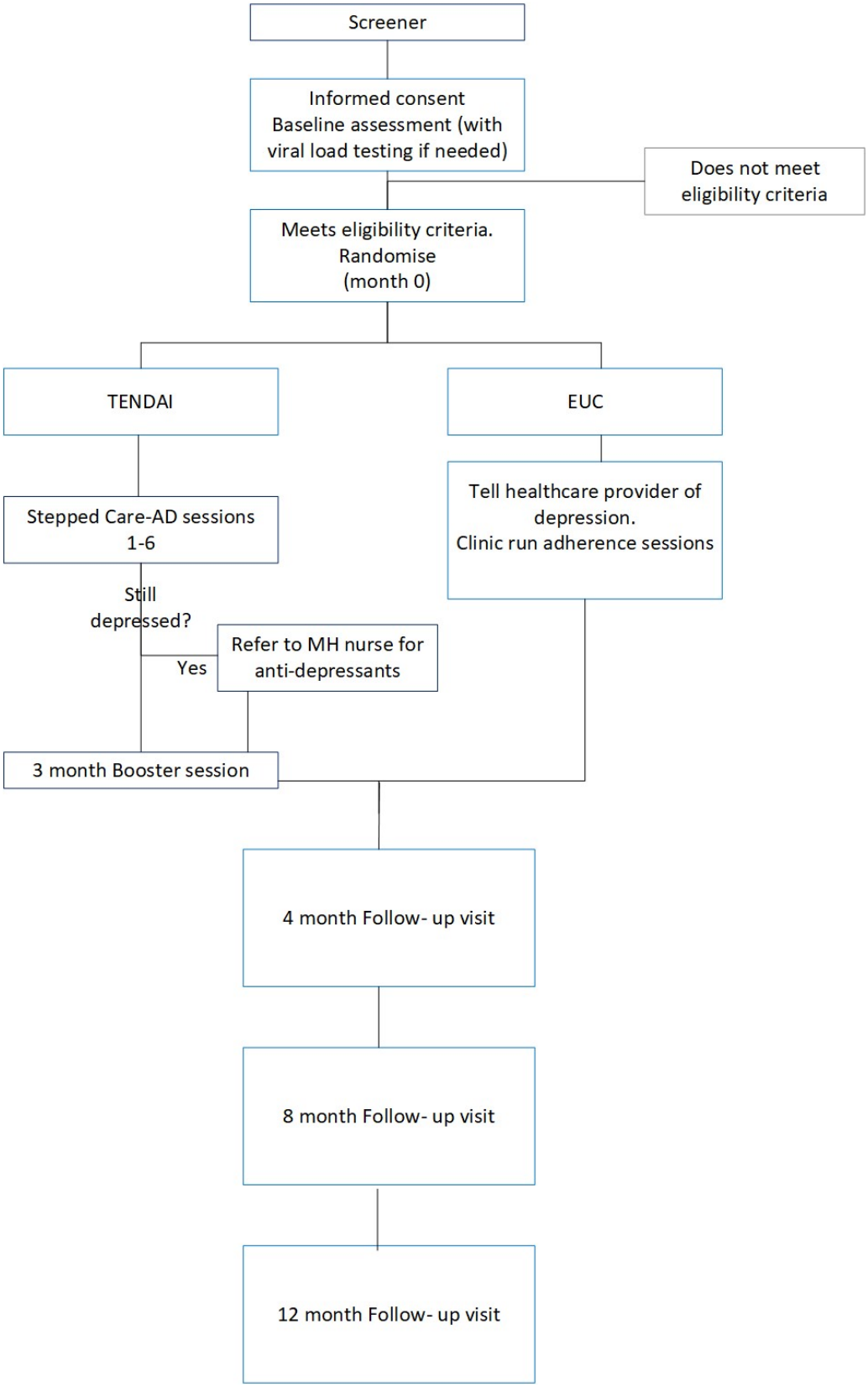
Moderation: we intend to investigate whether the effect of TENDAI vs EUC differs by sex, on the primary outcome of viral suppression, and the secondary outcomes of self-report adherence, and depression, see Sections 1.8.5 and 3.1.3. Other more exploratory moderation hypotheses may be published in another paper.

1.2 Trial design including blinding

A 12-month parallel arm randomised controlled trial of the TENDAI intervention on depression and ART adherence in adult patients living with HIV compared with enhanced usual care (EUC). Participants will be randomised 1:1 to 12-months treatment with either TENDAI or EUC. Randomisation, which will be stratified by site as the study will now take place in the Chitungwiza Central Hospital as well as the Marondera Provincial Hospital, will be conducted using a variable block randomisation schema (using Sealed Envelope) coordinated through the trial REDCap database. Only the Zimbabwean site Project Manager and the trial Database Manager have the ability to randomise participants. Eligibility for randomisation is confirmed on a weekly cross-site call, which involves the Zimbabwe study team, the study Principal Investigators, and study Clinical supervisors. The principal investigators, local and London programme managers, data manager and interventionists are unblinded. Blinded independent assessors will administer the PHQ-9, EQ-5D-3L, self-report adherence questionnaires at follow-up. The senior statistician will be fully blinded, and the junior statistician will be unblinded.

Figure 1. Trial design flow diagram

Schematic diagram of flow of participants (potential and actual) through the pre-trial assessment and trial. Please see the CONSORT diagram (Figure 2) for detail on how this will be reported.



1.3 Eligibility screening

Eligibility for the trial is assessed at an initial screening visit, then further assessed at the baseline visit.

1.3.1 Inclusion criteria

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

1.3.2 Exclusion criteria

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

1.4 Method of allocation of groups

Patients will complete baseline measures after providing informed consent to take part in the trial. Approximately two weeks after baseline assessments are complete, eligible individuals will be randomised to one of the trial arms using a variable block randomisation procedure. Randomisation will be done at the patient level in a 1:1 ratio and will be stratified on site (using the Sealed Envelope schema coordinated via REDCAP).

1.5 Duration of the treatment period

For the TENDAI group, 6 sessions will be delivered, one per week, with one booster session in week 12 post-randomisation. For the EUC group, there are 3 adherence counselling sessions. Providers of EUC are all trained in the WHO mhGAP guidelines for depression care and are free to follow this as per their preference and training. The antidepressant drug Fluoxetine is available for TENDAI providers and for EUC providers to prescribe.

1.6 Frequency and duration of follow-up

Participants will complete baseline measures prior to randomisation. Follow up measures will be completed at 4, 8 and 12 months post randomisation. Please see section 5 SCHEDULE OF ASSESSMENTS AND MEASURES for details and the data collection schedule.

1.7 Visit windows

An overview of the trial schedule is shown in Figure 1. Trial design flow diagram.
Randomisation will be done after completing baseline measures which are listed in section 5 SCHEDULE OF ASSESSMENTS AND MEASURES. There is no specified time window between the baseline visit and randomisation.

Treatment should be initiated as early as possible after randomisation. There is no specified time window. For the TENDAI group, sessions should be provided weekly (any day) between weeks 1 to 6 following randomisation, plus a booster session in week 12 following randomisation.

Follow-up visits should be no earlier than 30 days prior to the expected visit date, no later than 60 days after the expected visit date for 4 and 8 month follow up assessments, and no later than 120 days after the expected visit date for the final 12 month follow up. Visit window data will be summarised (see section 3.1.4.1); data collected outside the visit windows will still be used.

1.8 Measures

1.8.1 Baseline measures

The following measures are recorded at baseline (see Section 5,Table 5.1): MINI (depression), PHQ-9 (depression), PCL-5 (PTSD), medications used, recent or current pregnancy, current comorbid illness, Alcohol Use Disorders Identification Test (AUDIT), CD-4, viral load (blood plasma), DBS for ART detection, Self-report adherence (AQ), pharmacy refill adherence, mode of HIV transmission, depression treatment plus non-study therapy, Drug Use Disorders Identification Test (DUDIT), Social support (SS), HADS anxiety subscale, Adherence Self-Efficacy scale (ASES), Barriers to AntiRetrovial Adherence (BARTA), Problem Solving Skills subscale (PSSS), HIV related dementia scale (IHDS). COVID-19 measures were also added in March 2021.

Sociodemographic measures recorded at baseline include: age, sex, relationship status, educational history and level attained, income, main job, household assets. See section 2.2 for a list of the baseline variables that will be described in the primary paper.

Health economic outcomes are also recorded; CSRI and EQ5D3L.

1.8.2 Primary outcome measure

The primary outcome is viral suppression (<1000 copies/mL) at 12 months follow-up. The recorded viral load will be coded into a binary not suppressed/suppressed variable. Those missing viral load data where the medical or death records indicate a likely high viral load or AIDS related death will also be considered to be not suppressed – see also section 3.1.1. Viral suppression will be taken from the result recorded by the hospital if recorded within the 30 days prior to the 12 month post-randomisation visit date or will be assessed from a blood sample (plasma) collected by the trial team at the 12 month post-randomisation visit.

1.8.3 Secondary outcome measures

Secondary outcomes are:

1. Continuous depression score measured using Patient Health Questionnaire (PHQ) at 12 months post randomisation.
2. Adherence using pharmacy refill which will be recorded as a percentage adherence over the past month at 4, 8 and 12 months post randomisation. Adherence will be coded into a binary variable reflecting at least 90% adherence or not – see Section 3.1.2 for more detail.
3. Adherence using self-reported adherence to ART medication using a self report questionnaire scale (Wilson et al) measured at the 4, 8 and 12 months post randomisation visit. See Section 3.1.2 for more detail.
4. Continuous log (base 10) viral load copies/mL at 12 months using hospital records if recorded within the 30 days prior to the 12 month post-randomisation visit date or will be assessed from a blood sample (plasma) collected by the trial team at the 12 month post-randomisation visit.

1.8.4 Mediators of treatment effects

Hypothesised mediators of (a) the effect of TENDAI on depression and adherence outcomes, i.e. social support, PSSS and ASES, are recorded at baseline, 4 8 and 12 months. Hypothesised mediators of (b) the effects of TENDAI on viral suppression, i.e. depression, pharmacy refill, and blood sample measures of adherence are recorded at 4, 8 and 12 months. The social support, PSSS and ASES and dried blood spot measure of adherence that feature only in the mediation analysis will not be summarised in the main paper and so will not be referred to again in this SAP. The depression and pharmacy refill measures of adherence that will be studied as mediators of the effect of TENDAI on viral suppression are also secondary outcomes in the main trial. Mediation will not be reported in the primary trial paper and will not be discussed further in this document.

1.8.5 Moderators of treatment

The effect of the baseline moderator, sex, on the primary outcome of viral suppression, and the secondary outcomes of self-report adherence (Wilson et al) and depression will be tested. Moderation of the treatment effect by sex will be assessed for the main paper, and so methods for this analysis are discussed in this SAP (please see section 3.1.3). Further exploratory moderators household assets (BARTA) and depression severity mentioned in the protocol will be explored in further analyses which are beyond the scope of this SAP.

1.9 Sample size estimation

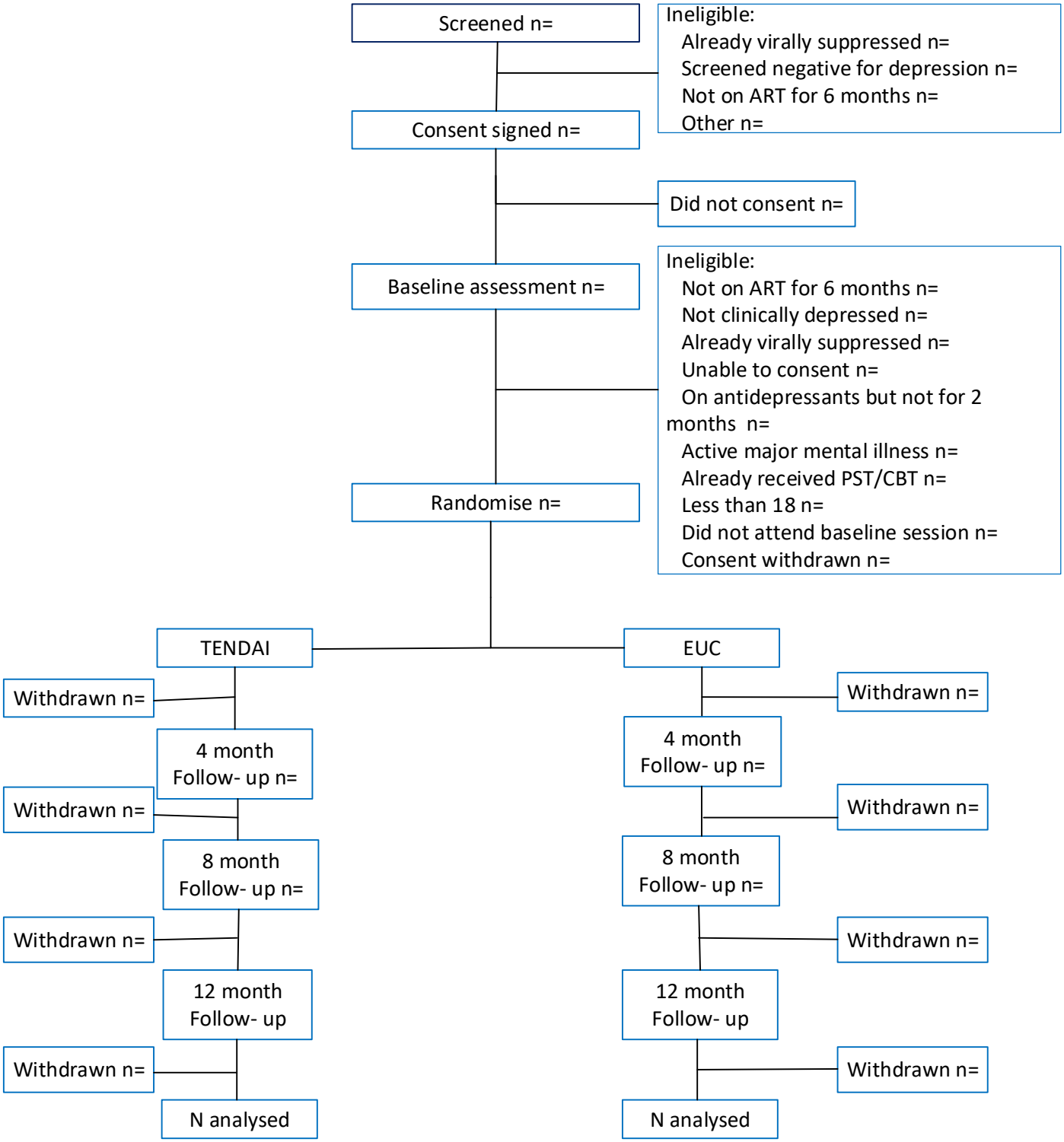
A sample size of 290 participants will provide 85% power to detect an absolute difference of 20% or more in achieving viral suppression (e.g. 45% in the EUC arm vs. 65% in the intervention arm) at 12-months follow-up. This is based on a two-sided Fisher's exact test with $\alpha = 0.05$ and allowing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

2. Data analysis plan – Data description

2.1 Recruitment and representativeness of recruited patients

A CONSORT flow chart will be constructed (Moher et al) – see Figure 2. This will include the number of eligible patients, number of patients agreeing to enter the trial, number of patients refusing, then by trial arm: the number continuing through the trial, the number withdrawing, the number lost to follow-up and the numbers excluded/analysed. The reasons for ineligibility/numbers not consenting following screening will be shown, as will the reasons for not being randomised following baseline.

Figure 2. Template CONSORT diagram for TENDAI trial



2.2 Baseline comparability of randomised groups

The measured baseline variables are given in section 1.8.1. Baseline variables will be described by trial arm and overall: means and standard deviations/medians and interquartile ranges for continuous variables that are normally distributed/not normally distributed, and frequencies and proportions for binary or categorical variables. The list of baseline variables we will describe is as follows: recruitment site, age, sex, relationship status, educational level attained, for those that have attained less than secondary school: years of primary school completed and years of secondary school completed, whether the participants have a job that provides income, whether the participants have a job that provides goods, occupational class, likely coded as unemployed/unskilled/skilled non-professional/professional, 1st, 2nd or 3rd line ART prescribed. No statistical testing of the baseline differences between randomised groups will be done.

2.3 Completion of allocated treatment, treatment fidelity and treatment experience

2.3.1 Completion of allocated treatment and treatment fidelity

The number of therapy sessions attended by participants in the TENDAI arm will be reported using the median and interquartile range.

We define completing the TENDAI treatment as completing at least four therapy sessions. Sessions are given in a pre-specified order such that a participant can only complete the fourth session of therapy once they have completed the first, second and third sessions or therapy, in that order. There is no definition of completion of therapy in the EUC arm. We will summarise the number and proportion completing at least four therapy sessions.

2.3.2 Treatment experience

The number and proportion of participants withdrawing from treatment only not the overall trial (for withdrawals, please see section 2.4) will be summarised for the TENDAI group only as well as by their reasons for withdrawing from treatment.

2.4 Loss to follow-up and other missing data

The number and proportions of participants missing each primary and secondary outcome variable will be summarised by trial arm and overall at each time point. The numbers and proportions withdrawing from the trial (i.e. actively state they are unwilling to provide any further research data) will be summarised by their reasons for withdrawal from the trial at each assessment time point by trial arm and overall.

2.5 Adverse event reporting

Adverse events (AE), and serious adverse events (SAE) will be summarised as number of events and number of people having events by trial arm and overall.

2.6 Scoring of questionnaire outcomes

See Appendix 1 for details on scoring of all outcome measures.

2.7 Descriptive statistics for outcome measures

The primary and secondary outcomes will be summarised at baseline, 4, 8 and 12 months, where the outcome is recorded at that timepoint (see sections 1.8 and 5 for details of the timepoints at which measures are recorded), these are: proportion with viral suppression, PHQ-9 score, adherence measured using (a) self-report, (b) pharmacy refill, and log viral load. Means and standard deviations or medians and interquartile ranges will be used for the continuous PHQ-9 and self-report adherence variables. Frequencies and proportions will be used to describe the binary/categorical viral suppression and adherence variables. We will also summarise the frequency and proportion of individuals switching medications between each time point.

3. Data analysis plan – Inferential analysis

3.1 Main analysis of treatment differences

The main statistical analyses will follow the intention to treat principle as much as possible. The senior statistician will remain fully blind until an initial draft of the primary analysis report is complete and needs to be checked. The trial

statistician will be unblinded. Group difference estimates between TENDAI and EUC and associated 95% confidence intervals will be reported from models appropriate to the measurement schedules and nature of the outcome in question, i.e. depending on whether the outcome is continuous or categorical. The models that will be used are outlined in the following sections. Where the outcome variable is recorded at baseline it will generally be included in the analysis model as a covariate unless stated otherwise. The significance level for the difference between TENDAI and EUC on the primary outcome will be 5% (two-sided). This significance level will also be used for the secondary outcomes, but the reader will be alerted regarding the impact of multiple testing.

Previous therapy trials (e.g. Everitt et al) have found that the post-randomisation completion of therapy variable was predictive of missingness of the primary outcome. We will therefore consider multiple imputation (MI) for the primary outcome only if there are post-randomisation variables that predict missing primary or secondary outcome data (see section 3.1.4.5 for the variables that will be considered). We will not consider multiple imputation where there are no post-randomisation variables that predict missing data, nor will we consider MI if less than ten percent of the outcome data are missing (Dong and Peng). The former is the usual/recommended approach in trials where independent variables (i.e. trial arm, time point, stratification factors) are generally complete, and imputing missing outcomes only adds variability/noise (Sullivan et al). For outcomes which are measured repeatedly, missing data in post randomisation assessments will be handled by fitting mixed models using maximum likelihood methods. Valid inferences are provided by this method assuming that the missing data mechanism is ignorable, that is, missing at random (MAR) and providing that all predictors of missing data are included as covariates in the model. To include such predictors of missing data, we will assess pre-specified baseline variables (see Section 3.1.4.5 Missing outcome data) to identify which measures are predictive of missing outcomes. If we use multiple imputation, these baseline variables will be included in the imputation but not analysis models. If we do not use multiple imputation, we will include these baseline variables as additional independent variables in the PHQ-9, self-report adherence and log viral load outcome analysis models described in sections 3.1.1 and 3.1.2. More detail on the handling of missing data can be found in section 3.1.4.5.

3.1.1 Analysis of primary outcome

The viral load data will be coded into a binary variable as follows: <1000 copies/mL (suppressed) or >=1000 copies/mL (not suppressed), please also see Appendix 1. Where the viral load data are missing at 12 months and the individual has died, the data will be left missing unless it is apparent from medical or death records that the person died due to high viral load or death was clearly AIDS related, in which case we will code them as not suppressed. The odds ratio at 12 months (and associated 95% CI) for <1000 copies/mL for TENDAI vs EUC will be estimated using a logistic regression model with the 12 month measure as the dependent variable, and trial arm as the independent variable, as well as the site stratification variable. We will fit two models, the one just described excluding baseline log viral load, and another including this as an independent variable, so will present odds ratio estimates both marginal and conditional with respect to baseline viral load. Moderation of treatment effects by sex will be assessed in these two final model backgrounds as outlined in Section 3.1.3.

3.1.2 Analysis of secondary outcomes

The mean difference at 12 months (and associated 95% CI) in PHQ-9 between TENDAI and EUC, and a standardised effect size, will be estimated using a linear mixed effects model with the 4, 8 and 12 month measures as dependent variables; a random intercept at the participant level, with a random slope if warranted (assessed via likelihood ratio test); baseline PHQ-9, trial arm, time, and trial arm by time interaction terms as independent variables; as well as the site stratification variable. Note for this PHQ-9 outcome that while we will include all post-randomisation measures as dependent variables in the model in order to account for missing data, we will not present treatment difference estimates for 4 and 8 months (as per the trial objectives/outcomes).

Pharmacy refill data will be recoded into a binary variable: greater than or equal to 90% adherence in the past month or less than 90% adherence in the past month. Please refer to Appendix 1 – Scoring of outcome measures. The odds ratio at 4, 8 and 12 months (and associated 95% CI) for >=90% pharmacy refill adherence between TENDAI and EUC will be estimated using a logistic mixed effects model with the 4, 8 and 12 month measures as dependent variables with a random intercept at the participant level, consideration of a random slope variable and similar independent variables as those described for PHQ-9. Please see the end of the section for some further details on the modelling of this binary variable.

Self-report adherence (Wilson et al) will be scored as described in the paper and modelled as described for PHQ-9.

The mean difference in log copies/mL of viral load at 12 months (and associated 95% CI) between TENDAI and EUC will be estimated using a linear regression model with the log viral load at 12 months as the dependent variable,

baseline log viral load and trial arm as independent variables, as well as the site stratification variable. Undetectable viral loads will be set to half the viral detection load limit of the Marondera Provincial Hospital lab machine, which is 15.

The logistic mixed effects models that will be used for the pharmacy refill adherence outcome are preferred on one hand because they have useful missing data properties. These will provide subject-specific effects. However, these subject specific conditional effects can be larger, sometimes appreciably larger, than either the crude odds ratio or the adjusted population-averaged marginal effects that would be obtained using Generalised Estimating Equation models (Hu et al). We will present both the conditional estimates from the mixed effects models, as well as the marginal estimates using GEE models with robust standard errors. We will focus on the conditional effects from the mixed models in the main paper, unless there is more than a two-fold difference, in which case we will focus on the GEE model results.

3.1.3 Moderation analysis

We plan to explore treatment effect moderation on the primary outcome of viral suppression at 12 months post-randomisation, and the secondary outcomes of self-report adherence and PHQ-9 depression by the putative moderator sex. We will assess moderation separately for each outcome as follows. We will add the sex variable to all models, then will add a sex by trial arm interaction term to the primary viral load outcome model, and a sex by trial arm by time term to the self-report adherence model. For PHQ-9 depression, we will have only a sex by trial arm term and will not include time in the interaction term in order to provide the average treatment difference over the outcome period. There will be considered to be moderation if the overall interaction term p-value is less than 0.05. If sex is a significant moderator, in addition to presenting overall treatment effects as per Sections 3.1.1 and 3.1.2, we will also present treatment effects by levels of the moderator.

3.1.4 Statistical considerations

3.1.4.1 Time points

Outcomes are measured at months 4,8, and 12 months after randomisation. Follow-up visits should be completed at no more than 1 month before the expected visit and at no more than 2 months after. We will plot histograms of the time post-randomisation of the visits and will report the proportion of research follow-up visits which are outside of the expected visit window by trial arm and assessment time point. The time windows will be summarised descriptively using means and standard deviations or medians and interquartile ranges as appropriate. There are no set time windows for the acceptable time window for the time from baseline to randomisation and from randomisation to start of treatment.

3.1.4.2 Stratification and clustering

Randomisation will be stratified by site and the randomisation stratifier will be included in all models as a covariate.

For some data, the data structure is longitudinal with repeated measures for continuous and binary outcomes (see table 5.1 for details). The correlation of observations within participants will be accounted for by using mixed effects models with a random intercept at the participant level (or possibly generalised estimating effects models) as per Section 3.1.

3.1.4.3 Missing items in scales and subscales

The number (%) with complete primary and secondary outcome data will be reported by trial arm and assessment time point and overall.

Where the primary publication for a questionnaire does not give instructions for how to deal with missing data, the total pro-rata score will be calculated provided that the level of missingness at the item level is less than 20%. In this way, the total score will be calculated provided that at least, for example, five out of six items are present. If five items are non-missing, the mean of these five will be used to impute the sixth. Where guidance is available it is detailed in Appendix 1 for a questionnaire.

3.1.4.4 Missing baseline data

There should be little missing baseline data as it should generally be complete prior to randomisation. Where there is missing baseline viral load, PHQ-9, self-report adherence, or pharmacy refill adherence data, simple mean imputation will be used to impute those data (White and Thompson) prior to any further coding/dichotomisation of variables as follows: viral load – viral copies/mL, PHQ-9 – the total score, self-report adherence the total score, pharmacy refill - the percentage adherence.

3.1.4.5 Missing outcome data

Where there are repeated post-randomisation outcome measures, missing outcome assessments will be dealt with by fitting appropriate models to all the available data using maximum likelihood methods or quasi-likelihood methods (Generalized Linear Mixed models). Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or MAR), i.e. all predictors of missing data are included. We will seek baseline predictors of missing data and include them as per Section 3.1. Also as mentioned in Section 3.1, we will only consider multiple imputation (MI) if post randomisation variables are found to be predictive of missing viral load outcome data (Sullivan et al), so we will assess a few pre-specified post-randomisation variables to see if they predict missing outcome data.

Baseline variables predictive of missing viral load data at 12 months.
A binary variable coding whether any primary or secondary outcomes are missing at any time point will be prepared and used as the dependent variable in a logistic regression model. The independent variables in the logistic regression model will be trial arm, site and the baseline covariate under investigation. This will be repeated for each of the baseline variables of interest. The following baseline variables will be tested as they are thought to be likely predictors of missing viral load data at 12 months: age, relationship status, education level (recoded as a single variable), income (recoded as a single variable), baseline self-report adherence to ART, baseline viral load, baseline PHQ-9 depression, access to mobile phone. Recoding of variables is described in Appendix 1 scoring of outcome measures. Each variable will be considered to predict missing viral load data if there is a significant relationship at a 5% level.

Post-randomisation variables predictive of missing viral load data at 12 months.
This will be assessed in a similar way to that used to identify which baseline variables predict missing outcome data. We will assess whether completion of therapy (in the TENDAI arm only) and self-report ART adherence at 12 months are predictive of missing data.

If there are post-randomisation variables that predict missing outcome data, we will impute a number of datasets equal to the percentage missing data in the primary viral load outcome (Dong and Peng) or 50 datasets (whichever is higher). As well as the relevant variables from Sections 3.1.1 and 3.1.2, the imputation model will include all baseline and post-randomisation variables we find to predict missing outcome data and the putative moderating variable sex, imputing the trial arms separately as recommended by Thomas et al when moderation analysis is planned. We will endeavour to construct the imputation models as described, but if not viable, we may need to consider a set of simpler imputation models (i.e. when imputing with interaction terms we may need to remove some other variables from the imputation model). Where MI is used, we will produce estimates from both the complete case and MI data and include both in the statistical report, with the latter being the main estimates reported in the primary publication. If there are no post-randomisation variables that predict missing outcome data, but there are baseline variables predictive of missing data, these will be included in the non-logistic primary and secondary outcome analysis models (i.e. PHQ-9, self-report adherence, log viral load).

3.1.4.6 Method for handling multiple comparisons

There is a single primary outcome and we do not plan to adjust for multiple comparisons for the secondary outcomes.

3.1.4.7 Method for handling non-compliance (per protocol analyses)

The analysis of the primary outcome of viral suppressions will be duplicated excluding participants who did not complete the TENDAI intervention as per section 2.3.1. There is no definition of completion for the EUC arm, therefore all EUC participants could potentially be included in this analysis. Participants who were found post randomisation to have been enrolled in error/to have been ineligible will also be excluded from this analysis.

3.1.4.8 Model assumption checks

The linear regression and linear mixed effects models assume normally distributed outcomes; this will be checked when describing the data and if substantial departures from normality occur, transformations will be considered. Residuals will be plotted to check for normality and inspected for outliers.

3.1.5 Sensitivity analyses

3.1.5.1 Viral load primary outcome assumptions

We will undertake two sensitivity analyses on the primary binary viral load outcome, repeating the analysis described in Section 3.1.1:
1) excluding the individuals that died with missing viral load and were coded as non-suppressed (died due to high viral load or death was clearly AIDS related),
2) assuming the medical/death data were incorrect and coding these individuals (that died with missing viral load and were coded as non-suppressed) as virally suppressed.

3.1.5.2 COVID19

We will describe the baseline characteristics of participants as described in Section 2.2 also split by randomisation date before and after the pandemic started on 30th March 2020. We will also describe the baseline measures of the primary and secondary outcomes split by randomisation date before and after the pandemic started. We will summarise post-randomisation measures of the primary and secondary outcomes as described in Section 2.7 also split by collected before and after the pandemic started on 30th March 2020.

We do not expect that between group differences would be altered by COVID, but we will perform the following analysis to explore this. As the pandemic has progressed somewhat differently in Zimbabwe as compared to the UK, with different periods of lockdown, the study team have been keeping track of key dates and we expect to be able to construct a variable of this sort: 1 = pre-COVID, 2 = key post COVID period 1, key post COVID period 2, etc. These key periods should align with events like start and stop of lockdowns, curfews and changes to local transport. We will then perform an analysis on the primary binary viral load outcome and the secondary log viral load outcome where we add a trial arm by COVID period interaction term. If an omnibus test across the interaction term parameters is significant at $p < 0.05$, we will report between group differences in these two variables separately for the different time periods.

3.2 Planned subgroup analyses

No formal subgroup analyses are intended as the study is not powered to detect treatment effects for subgroups.

However, we do plan to explore treatment effect moderation on the primary outcome of viral suppression at 12 months post-randomisation, and the secondary outcomes of pharmacy refill adherence, self-report adherence and PHQ-9 depression (all at 12 months) by the putative moderator, sex – please see section 3.1.3.

3.3 Interim analysis

No interim analysis is planned in this study.

4. Software

Data management: An online data collection system for clinical trials REDCAP will be used. This is hosted on a dedicated server at Massachusetts General Hospital (MGH) and managed by the MGH team. The MGH Data Manager will extract data periodically as needed.

Statistical analysis: Stata v16-17 will be used for data description and the main inferential analysis.

5. SCHEDULE OF ASSESSMENTS AND MEASURES

Table 5.1 Data collection points timeline

	BL	Rand	4M	8M	12M
Consent and Staff	X				
Demographics	X				
COVID-19 Screening	X		X	X	X
PHQ9	X		X	X	X
EQ-5D-3L	X		X		X
Self-Report Adherence (Major Assessment)	X		X		X
Self-Report Adherence (Weekly Visits)					
Adherence Self-Efficacy	X		X		X
Medications	X		X		X
Pharmacy Refill	X		X		X
Mode of Transmission	X				
Biological Markers	X				X
BARTA	X		X	X	X
PCL-5 + LEC-5	X		X	X	X
AUDIT	X		X	X	X
DUDIT	X		X	X	X
HADS Anxiety Subscale	X		X	X	X
Social Support	X		X	X	X
The Client Services Receipt Inventory (CSRI)	X		X	X	X
MINI	X				
International HIV Dementia Scale (IHDS)	X				
Bipolar/Psychosis Screener	X				
COVID-19 Measures	X		X	X	X
P4 Screener	X		X	X	X
Dried Blood Spot for ART Adherence		X	X	X	X
Randomisation		X			

Notes
An adapted 1-week version of the PHQ-9 is also recorded at therapy sessions 3,4,5, and 6 for participants randomised to TENDAI. These records will not be used in the analyses described in this document.
PCL-5, Depression treatment and non-study therapy are recorded at all trial visits, all trial visits, and baseline only.
HIV Related Dementia Scale is recorded at baseline only. These records will not be used in any analysis described in this analysis plan and will not be scored.

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Appendices

Appendix 1 – Scoring of outcome measures

For details of measures and scoring please refer to the TENDAI Codebook_v1.1_12th October 2021_updated refs.

Appendix 2 – Acronyms and abbreviations

Below is a list of questionnaires/variables being administered/measured in the trial, along with the acronym or abbreviation that will be used in this document. Section 5 shows the data collection schedule.

Audit C - Alcohol checklist,
ASES – Adherence Self-Efficacy Scale,

AQ – adherence questionnaire,
ARV – medications list for anti-retroviral treatment,
BARTA – Barriers to AntiReTroviral Adherence for people living with HIV in Zimbabwe
Rx-AntiD – other medications for depression (including anti-depressant),
CSRI – Client Services Receipt Inventory,
CD4 – absolute CD4 cell number,
DBS – Dried Blood Spot,
DBS-ART – presence of ART drugs measured by DBS,DFD – depression free days and participant value,
DUDIT – Screen for substance abuse (in Shona),
EQ5d -Shona version of EQ5D-3L measuring quality of life,
MINI 7.0.1 - Diagnostic interview for comorbid mental health disorders,
PCL-5 – PTSD checklist,
PHQ-9 – depression,
PRC – pharmacy refill counts – measure of adherence,
PSSS – Problem Solving Skills subscale (measuring problem solving),
SS – Social support locally developed measure,
VL – viral load from medical record,