HIV+D Statistical Analysis Plan

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TABLE OF CONTENTS

INTRODUCTION

Depressive disorders are common among persons living with HIV (PLHIV), and have been associated with poorer adherence to treatment and increased risk behaviours [1-3]. While high-income countries frequently integrate mental health care services within HIV treatment, this remains uncommon in lower-income settings such as Uganda. In response, the *Uganda National HIV and AIDS Strategic Plan 2020-21 2024-25* has called for the assessment and management of depression among PLHIV as a strategic objective [4]. The HIV+D study is a cluster-randomized trial assessing the effectiveness and cost-effectiveness of a model integrating depression management within HIV services at improving mental health and HIV-related outcomes [5].

In this statistical analysis plan (SAP), we present the plan for analysis of mental health and HIV outcome data. The plan for analysis of economic data will be presented separately.

Research hypotheses

The study hypotheses are:

- The HIV+D intervention will improve the clinical and functional depressive disorder (DD) outcomes in persons living with HIV (PLWH) with DD.
- The HIV+D intervention will improve clinical symptoms of generalised anxiety disorder (GAD), adherence to ART, will be cost-effective and will improve uptake and acceptability of depression management in public HIV care services.

This Statistical Analysis Plan (SAP) covers the analysis of the effectiveness of HIV+D at improving clinical and functional DD, GAD, and ART adherence. Economic analyses assessing the cost effectiveness of the intervention will be covered in a separate SAP.

STUDY DESIGN

Trial design

The trial is a 2 parallel-arm cluster randomized trial. Clinics were randomised 1:1 to receive the HIV+D intervention or enhanced usual care (EUC). The trial results will be reported using the CONSORT guidelines extension for reporting cluster randomised trials [6].

Selection of clinics and participants

The trial was conducted in three districts within Uganda: Kalungu, Masaka, and Wakiso. Within these districts, all hospitals and level III-IV health facilities (N=51) were eligible for randomisation. Note that 2 eligible health facilities were co-located on the same site (TASO Masaka and Masaka Regional Referral Hospital) – one of these (TASO Masaka) was selected at random for removal before randomisation.

Within health facilities in both arms, trained lay health workers (LHW) provided a health talk about depression and screened facility attendees using the PHQ-2. If the attendee screened positive on the PHQ-2 (PHQ-2≥3), the LHW administered the PHQ-9. Clients screening for depressive disorders using the PHQ-9 (PHQ-9≥10) were eligible for the study. Additional eligibility criteria included:

- Age 18 years or older
- On ART for at least 6 months
- Attending the HIV clinic at the facility

- Medically stable at the time of the study (i.e., not requiring emergency admission)
- Conversant in English or Luganda
- Willing to be visited at home as needed

Clients meeting the eligibility criteria were excluded from the study for the following reasons:

- Have impairments that may hinder engagement with research protocol (deaf or hard of hearing, speech impaired, blind or partially sighted);
- Already receiving treatment for depression or other psychiatric treatment
- Have an alcohol use problem (defined as CAGE [7, 8] ≥2).

Consecutive attendees were screened until the daily target (4-5 PLHIV) was reached.

OUTCOME EVALUATION AND DATA DESCRIPTION

Primary outcome

The primary outcome for the study was mean DD severity score, measured using PHQ-9 at 3 months post-enrolment.

Secondary outcomes

Secondary outcomes included:

- Mean DD severity score, measured using PHQ-9 at 12 months post-enrolment
- Proportion with PHQ-9 score ≥9 at 3 and 12 months post-enrolment respectively. For this analysis, the numerator will include all respondents with PHQ-9 score ≥9 at the relevant time point and the denominator will include all respondents with a PHQ-9 measure.
- Mean GAD severity score, measured using GAD-7, at 3 and 12 months post-enrolment respectively
- Proportion with virological failure, defined as ≥400 copies/ml, at 12 months post-enrolment. The numerator will include respondents with virological failure based on the measure taken at the relevant time point and the denominator will include all respondents with a PHQ-9 measure.
- Proportion self-reporting missing at least 1 dose of ART in the past 3 days, at 3 and 12 months post-enrolment. The numerator will include all respondents answering 1 or more doses to the question “Doses of ARVs missed in the past 3 days”. The denominator will include all respondents with data on this measure..

Sample size calculation

The sample size was calculated to ensure sufficient power to identify differences in the primary outcome (mean PHQ-9 after 3 months of implementation), using standard methods for cluster randomized trials as detailed in Hayes and Moulton [9]. The formula calculates the number of clusters required for a given cluster size, effect estimate, and cluster coefficient of variation (k). We used a study-wide alpha=0.05, divided in two to reflect co-primary outcomes.

In calculating the sample size, we assumed the mean PHQ-9 among participants in the EUC arm would be 6, with within-cluster standard deviation of 4.4. The cluster coefficient of variation in both arms was assumed to be k=0.25; this was assumed to be a conservative

estimate for clustering of mental health outcomes and was informed by other studies [10]. We anticipated reaching a harmonic mean of 15 participants per clinic; the harmonic mean was used in this calculation to account for variability in cluster sizes [9]. Using these assumptions, with 20 clinics per arm we had 90% power to detect a 2-point mean difference in severity score (i.e. 6 in EUC vs 4 in HIV+D) with 97.5% confidence. This allows approximately 1 participant to be lost to follow-up in each clinic. For 80% power to detect the same difference, we need to recruit 9 participants/cluster.

Additional survey items

All participants were first screened for additional questions using the PHQ-2. Participants with PHQ-2≥3 [11] were considered for inclusion in the study.

- Sociodemographic data (i.e., educational attainment, religion)
- Alcohol use assessment and CAGE [7, 8]
- PHQ-9 [11, 12]

After ascertainment of eligibility, the following items were asked at baseline:

- GAD-7 [13]
- Health economics questionnaires including questions on patient costs, EQ-5D-5L assessing problems across multiple dimensions of health [14], and OxCAP-MH (Oxford capabilities questionnaire – mental health) [15]

Urine sample and HIV viral load results will be taken from patient files at 6 and 12 months post-enrolment.

For patients at risk of suicide, measured as answering positively to item 9 on the PHQ-9, a MINI instrument for determining suicidality will also be administered.

Duration of intervention

The intervention will be implemented for 12 months, with primary endpoint data collected after 3 months.

Trial arms, stratification, randomisation, masking

The trial will take place across 40 clinics in three districts (Kalungu, Masaka, and Wakiso) in Uganda.

Selection and randomisation of clinics

The unit of randomization was the clinic, and 50 clinics were eligible for inclusion in the study. Clinics were stratified into i) hospitals and large health clinics, including Health Centre IV, District Hospital, Regional Referral Hospital, and Private not-for-profit hospitals (n=13); and ii) smaller health clinics, including Health Clinic IIIs (n=37).

The initial selection of clinics to include in the study was completed by MN on 28 September 2020 using Stata/SE 16.1. All hospitals and large health clinics were included in the clinic selection, and 27 of 37 smaller health clinics were chosen at random to make up 40 in total. The random choice was conducted using a random number generator in Stata 16.1. Five alternate small clinics were selected at this time and numbered at random, in case selected clinics needed to be replaced.

Randomisation of selected clinics was completed by MN on 28 November 2020 using Stata/SE 16.1. 13 health centre IV's and 27 health centre III's were randomly allocated into arm A and arm B. In a second step, arm B was randomly assigned to the active arm. The randomisation summary is included as **Appendix A**. A public randomisation ceremony was not conducted due to restrictions related to the COVID-19 pandemic.

Because the study ended up requiring more than 5 alternate clinics, the remaining 5 clinics not initially selected as study or replacement clinics were randomly ordered as additional alternates on 18 May 2021. 2 clinics (1 in HIV+D arm and one in EUC arm) were replaced due to low recruitment rate.

Masking

Statisticians involved in the analysis (MN, IS, HW) will be masked to allocation until both data collection and the analysis of the primary outcome is complete. It was not possible to mask allocation for participants, or clinical staff, or data collectors because of the nature of the intervention and the role of data collectors as expert clients in the clinic. The data manager (WS) will not be masked.

STATISTICAL METHODS

All analyses will use mixed-effects regression methods appropriate for CRTs randomised at the community level with a large number of clusters [9]. Analysis of the trial outcomes will be by intention-to-treat which includes all participants randomised. A per-protocol analysis will also be conducted, and is described below.

Recruitment and representativeness of sample

A CONSORT flow diagram (**figure 1**) will illustrate participant recruitment and follow-up.

Comparability of arms

Before beginning analysis of the impact of the intervention, we will summarise baseline data by arm by type of health facility (hospital, health centre IV, health centre III), district of health facility, and by the following individual characteristics.

- Age
- Sex
- Marital status
- Religion
- Educational attainment
- Employment status
- Socioeconomic status measured using a principal components analysis of assets variables
- HIV viral load (≥200 copies/ml or <200 copies/ml)

Frequencies and percentages will be used to present categorical variables (See table 1). The study team will identify substantial differences between arms in terms of the above factors, and will adjust for these differences in adjusted outcome analyses. No formal statistical testing will be performed to examine differences in baseline characteristics between the trial arms, as any difference will be due to chance if the randomisation was correctly performed.

Loss to follow up
For analysis of primary and secondary outcomes, participants will be considered lost to follow up (LFU) as follows:

- Month 1: LFU if no contact after 6 weeks post month-1 scheduled visit date
- Month 3: LFU if no contact after 6 weeks post month-3 scheduled visit date
- Month 12: LFU if no contact after 1 month post month-12 scheduled visit date.

Potential reasons for LFU include moving away from the study area, refusing to participate, unable to be located, illness. Participants who end the intervention due to clinical counterindications will not be considered LFU.

For participants who return to the study after being LFU at a study visit, the study team will capture information on why the participant was unable to attend a study visit. Data from these respondents will be collected per the usual study protocol. Outcome data collected outside the time periods described above (i.e., outcome data collected in week 7 post-month 3 visit date) will not be included in the primary outcome, but will be included in a sensitivity analysis.

Minimally- and fully-adjusted analyses
While fully analyses adjusted for imbalances at baseline will be considered the primary analysis, both unadjusted and adjusted analyses will be presented.

Minimally-adjusted analyses will be conducted using random-effects linear regression for continuous outcomes, and random-effects logistic regression for binary outcomes, with the random effect accounting for within-clinic clustering of respondents. All analyses will be adjusted for arm, baseline outcome values summarised at cluster level [16, 17] and stratification factors (hospital v. not hospital) as fixed effects. Fully adjusted analyses will be additionally adjusted for baseline imbalances in covariates, to be assessed before unmasking the data.

Analyses of continuous outcomes: The primary outcome (mean PHQ-9 at 3 months follow-up) will be modelled in minimally-adjusted analysis as:

$$PHQ9_{ij} = \beta_0 + \beta_1 arm_j + \beta_2 baselinePHQ9_j + \beta_3 hospital_j + u_{0j} + e_{0ij}$$

Where $PHQ9_{ij}$ represents the 3-month PHQ-9 score for participant *i* in clinic *j*; Arm_j represents an indicator of whether clinic *j* is in the EUC or HIV+D arm; $baselinePHQ9_j$ represents the participant's cluster's baseline PHQ-9 measure; $hospital_j$ indicates whether clinic *j* is a hospital/large health facility or not; u_{0j} represents the clinic-level random effect and is assumed to be normally distributed with mean 0 and variance σ^2_u; and e_{0ij} represents the individual-level residual and is assumed to be normally distributed with mean 0 and variance σ^2_e. The effectiveness of the intervention will be tested as H0: $\beta_1=0$.

Other continuous outcomes will be modelled similarly. The intervention effect will be presented as an adjusted mean difference between trial arms with a 95%CI.

Mixed-effect linear regression analyses will be completed using the *mixed* command in Stata 16.1. We will inspect residual plots (i.e., fitted fixed effects v. residual) to ensure model assumptions are met.

Analysis of binary outcomes: Analogous methods will be used to analyse binary outcomes using random-effects logistic models fitted using the *melogit* command in Stata 16.1, with quadrature checks to confirm that the random effect is appropriately specified

Of note, the estimates from random effects logistic models are interpretable as the effect of treatment on an individual in the median clinic (or cluster), not the population-level impact of treatment across all clusters [18]. The estimate generated using a random-effects logistic model will thus be useful in understanding the clinical impact of HIV+D treatment on an individual patient, but will not fully reflect the public health impact of implementing across all clinics. If the results of secondary outcomes analysis indicate that HIV+D has a moderate ($p<0.1$) impact on binary outcomes, we will conduct a sensitivity analysis using population average models (*xtgee* command in Stata) and present these results in an appendix. However, the results from fully adjusted random effects logistic models will represent the primary analysis of binary outcomes.

Missing data

Missing data on outcomes and key covariates will be assessed prior to analysis. In situations where >5% of data are missing, we will use missing data methods appropriate for random effects models [19]. Data will be assumed to be missing at random (MAR), and respondents with missing data will be described by clinic and key sociodemographic characteristics. We will use the *mi* command in Stata 16.1 to calculate multiple imputation (MI) models using linear or logistic regression models as appropriate. We will adjust for clinic and factors associated with missingness as fixed effects in imputation models, and 50 datasets will be imputed. Where MI models are used, these will be the primary analysis results, provided they are able to be estimated with no difficulty. Complete case analysis will be conducted and reported as a sensitivity analysis, and will be used as the primary analysis if there are difficulties obtaining estimates in the MI models.

Planned subgroup analyses

Differences in the effectiveness of the intervention in affecting primary and selected secondary outcomes (mean DD at 12 months, virological failure) will be assessed by sex of respondent, and binary categories of baseline severity of DD, and HIV viral load at baseline. Specific cut-points for categorising the continuous variables will be determined after reviewing the distribution of data at baseline. An interaction term ($arm_j \times X_{ij}$) will be added to the regression models as specified above, and the parameter on this interaction term will be assessed for statistical significance. All planned subgroup analyses will include adjustment factors as outlined for the fully adjusted models above. Stratified results by subgroup will be presented in tables.

Per-protocol analysis

A per-protocol analysis will be conducted to assess whether the respondents who completed the full intervention package had improvements on primary and secondary outcomes. Completion of the intervention will be defined as completing the full course of treatment, as defined using a completed HIV+D study discharge form. Clients who are removed from the HIV+D intervention for clinical reasons will not be censored [20].

We assume that non-adherence to the intervention will not occur at random, and will consider using inverse probability weighting methods to adjust for time-varying confounding due to incomplete adherence [20, 21].

Sensitivity analysis

Data collected from respondents outside the time period outlined for each data collection point (under “Loss to follow-up”, above) will be included as outcomes in a sensitivity analysis.

Additional analyses

Process measures measured within the trial arm will be summarized with frequencies and 95% confidence intervals. 95% confidence intervals will be adjusted for clustering by facility and stratification by type of facility using the *svy* commands in Stata.

Analysis of health economics outcomes will be covered in a separate statistical analysis plan.

Figures and tables

Figure 1 – CONSORT flow diagram

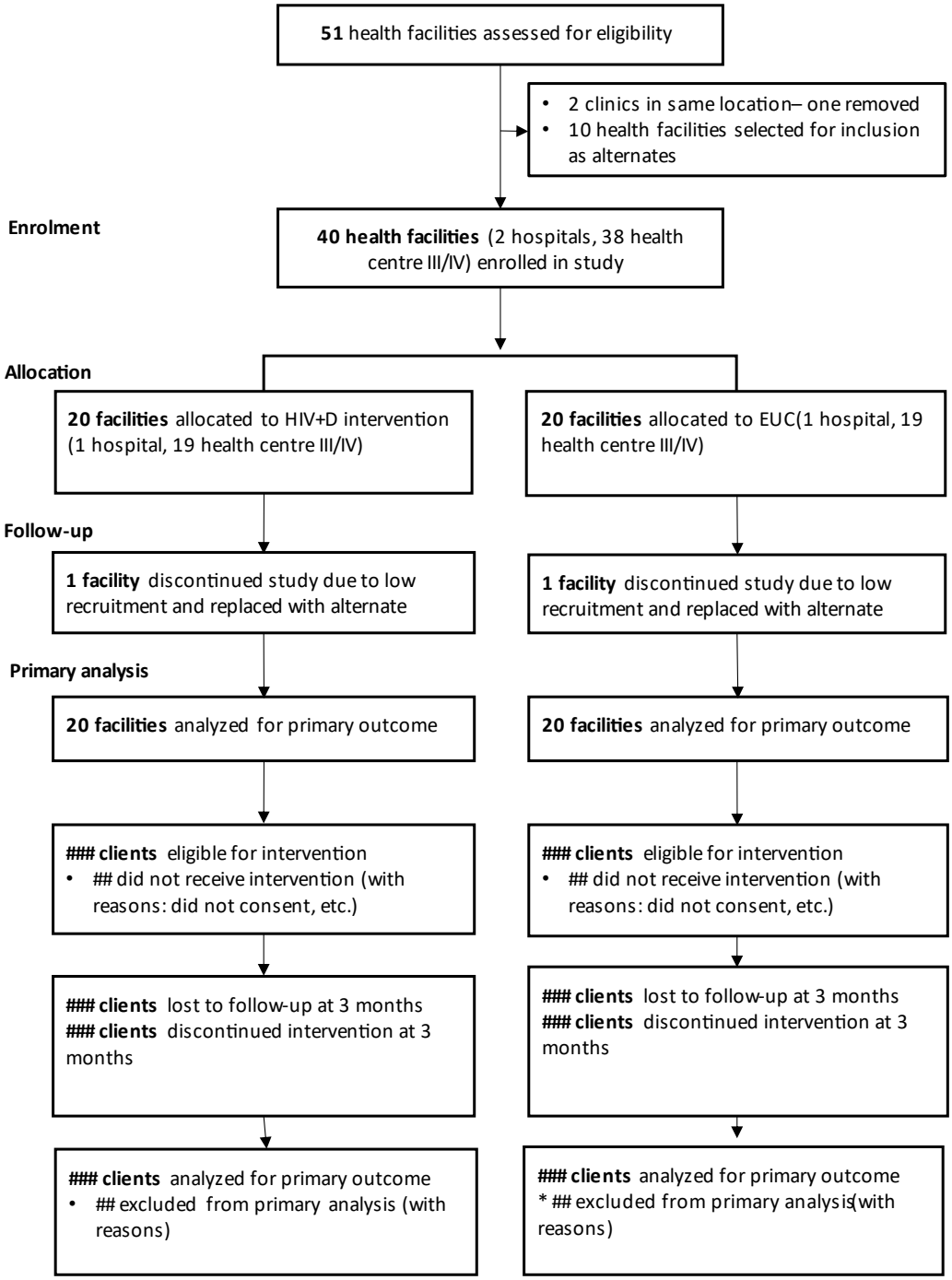

Table 1. Baseline characteristics of study population

	HIV+D (20 clusters, N=###)	SOC(20 clusters, N=###)
Facility-level (N=40)		
Total	20 (100%)	20 (100%)
Facility type		
Hospital	##.# (##.#)	##.# (##.#)
Health clinic IV	##.# (##.#)	## (##.#%)
Health clinic III	##.# (##.#)	## (##.#%)
District		
Kalungu	##.# (##.#)	##.# (##.#)
Masaka	##.# (##.#)	## (##.#%)
Wakiso	##.# (##.#)	## (##.#%)
Individual-level (N=###)		
PHQ-9 score (mean/SD)	##.# (##.#)	##.# (##.#)
Age (years)		
18-25	##.# (##.#)	##.# (##.#)
26-35	##.# (##.#)	##.# (##.#)
36-45	##.# (##.#)	##.# (##.#)
46-55	##.# (##.#)	##.# (##.#)
56+	##.# (##.#)	##.# (##.#)
Sex		
Female	##.# (##.#)	##.# (##.#)
Male	##.# (##.#)	##.# (##.#)
Marital status		
Never married	##.# (##.#)	##.# (##.#)
Married or living as married	##.# (##.#)	##.# (##.#)
Widowed	##.# (##.#)	##.# (##.#)
Separated or divorced	##.# (##.#)	##.# (##.#)
Educational attainment		
No formal education	##.# (##.#)	##.# (##.#)
Primary education	##.# (##.#)	##.# (##.#)
Secondary or tertiary education	##.# (##.#)	##.# (##.#)
Employment status		
??	##.# (##.#)	##.# (##.#)
??	##.# (##.#)	##.# (##.#)
Wealth index tertile*		
Lowest	##.# (##.#)	##.# (##.#)
Middle	##.# (##.#)	##.# (##.#)
Highest	##.# (##.#)	##.# (##.#)
Religion		
Catholic	##.# (##.#)	##.# (##.#)
Protestant (incl. SDA and “born again”)	##.# (##.#)	##.# (##.#)
Muslim	##.# (##.#)	##.# (##.#)
Other or no religion	##.# (##.#)	##.# (##.#)
HIV viral load		
≥200 copies/ml	##.# (##.#)	##.# (##.#)
<200 copies/ml	##.# (##.#)	##.# (##.#)

*Wealth index definition here

Table 2. Impact of HIV+D intervention on primary and secondary outcomes

Outcome	HIV+D mean (SD)	HIV+D (N)	EUC mean (SD)	EUC (N)	AMD	95% CI	p-value	k
Primary outcome: Mean PHQ-9 score at 3 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Secondary outcomes								
Mean PHQ-9 score at 12 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Mean GAD score at 3 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Mean GAD score at 12 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
	HIV+D n/N		**EUC n/N**		**OR**	**95% CI**	**p-value**	**k**
Proportion with PHQ-9≥9 at 3 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Proportion with PHQ-9 ≥9 at 12 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Proportion with virological failure at 12 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Proportion self-reporting missing at least 1 dose of ART in the past 3 days, at 3 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Proportion self-reporting missing at least 1 dose of ART in the past 3 days, at 12 months	## (##)	##	## (##)	##	###	(###, ###)	####	####

Table 3. Analysis of primary and selected secondary outcomes by subgroup

Outcome	HIV+D mean (SD) or n/N	EUC mean (SD) or n/N	AMD/OR	95% CI	p-value	Total	p-value for interaction
Sex							
Primary outcome: Mean DD severity score, measured using PHQ-9, after 3 months after enrolment							
Female	## (##)	## (##)	###	(###, ###)	####	####	####
Male	## (##)	## (##)	###	(###, ###)	####	####	####
Secondary outcomes							
Mean DD severity score, measured using PHQ-9, after 12 months after enrolment.	## (##)	## (##)	###	(###, ###)	####	####	####
Female	## (##)	## (##)	###	(###, ###)	####	####	####
Male	## (##)	## (##)	###	(###, ###)	####	####	####
Proportion with virological failure after 12 months after enrolment							
Female	## (##)	## (##)	###	(###, ###)	####	####	####
Male	## (##)	## (##)	###	(###, ###)	####	####	####
Baseline severity of DD							
Primary outcome: Mean DD severity score, measured using PHQ-9, after 3 months after enrolment							
10≤DD<20	## (##)	## (##)	###	(###, ###)	####	####	####
DD≥20	## (##)	## (##)	###	(###, ###)	####	####	####
Secondary outcomes							
Mean DD severity score, measured using PHQ-9, after 12 months after enrolment.	## (##)	## (##)	###	(###, ###)	####	####	####
10≤DD<20	## (##)	## (##)	###	(###, ###)	####	####	####
DD≥20	## (##)	## (##)	###	(###, ###)	####	####	####
Proportion with virological failure after 12 months after enrolment							
10≤DD<20	## (##)	## (##)	###	(###, ###)	####	####	####
DD≥20	## (##)	## (##)	###	(###, ###)	####	####	####
HIV viral load at baseline							
Primary outcome: Mean DD severity score, measured using PHQ-9, after 3 months after enrolment							
≥200ml	## (##)	## (##)	###	(###, ###)	####	####	####
<200ml	## (##)	## (##)	###	(###, ###)	####	####	####

Outcome	HIV+D mean (SD) or n/N	EUC mean (SD) or n/N	AMD/OR	95% CI	p-value	Total	p-value for interaction
Secondary outcomes							
Mean DD severity score, measured using PHQ-9, after 12 months after enrolment.	## (##)	## (##)	###	(###, ###)	####	####	####
≥200ml	## (##)	## (##)	###	(###, ###)	####	####	####
<200ml	## (##)	## (##)	###	(###, ###)	####	####	####
Proportion with virological failure after 12 months after enrolment							
≥200ml	## (##)	## (##)	###	(###, ###)	####	####	####
<200ml	## (##)	## (##)	###	(###, ###)	####	####	####

(Note that definitions of DD and HIV viral load subgroups subject to change)

Table 4. Process measures within all facilities

Process indicator	**HIV+D** **Mean (95% CI)**	**EUC** **Mean (95% CI)**
Patient satisfaction with depression care at 3 months post-enrolment*	##.# (##.#, ##.#)	##.# (##.#, ##.#)
Patient satisfaction with depression care at 12 months post-enrolment*	##.# (##.#, ##.#)	##.# (##.#, ##.#)
	n/N **Pct. and 95% CI**	
Proportion of enrolled clients receiving psychoeducation	##/### ##.# (##.#, ##.#)	##/### ##.# (##.#, ##.#)
Proportion of enrolled clients receiving at least 1 BA session	##/### ##.# (##.#, ##.#)	##/### ##.# (##.#, ##.#)
Proportion of enrolled clients receiving anti-depressant medication	##/### ##.# (##.#, ##.#)	##/### ##.# (##.#, ##.#)
Proportion of enrolled clients referred to mental health professional	##/### ##.# (##.#, ##.#)	##/### ##.# (##.#, ##.#)

***** Measured using scale presented in Edes and colleagues 2015 [22]

Table 5. Process measures within intervention facilities only

Process indicator	**HIV+D** **Median (IQR) or mean (95% CI)**
Number of BA sessions attended (median/IQR)	##.# (##.#, ##.#)
Fidelity assessment tool: Total (25 items)*	##.# (##.#, ##.#)
(1) Treatment specific skills (7 items)	##.# (##.#, ##.#)
(2) Beginning phase section (2 items)	##.# (##.#, ##.#)
(3) Middle phase section (4 items)	##.# (##.#, ##.#)
(4) Ending phase section (2 items)	##.# (##.#, ##.#)
(5) General skills (10 items)	##.# (##.#, ##.#)

* Measured using (citation for scale measure)

WORKS CITED

1. Douaihy A, Singh N. Factors affecting quality of life in patients with HIV infection. The AIDS reader. 2001;11(9):450-4, 60.
2. Farinpour R, Miller EN, Satz P, Selnes OA, Cohen BA, Becker JT, et al. Psychosocial risk factors of HIV morbidity and mortality: findings from the Multicenter AIDS Cohort Study (MACS). Journal of clinical and experimental neuropsychology. 2003;25(5):654-70.
3. Langford SE, Ananworanich J, Cooper DA. Predictors of disease progression in HIV infection: a review. AIDS research and therapy. 2007;4(1):1-14.
4. Uganda AIDS Commission. The National HIV and AIDS Strategic Plan. Kampala: Uganda AIDS Commission, 2020.
5. Kinyanda E, Kyohangirwe L, Mpango RS, Tusiime C, Ssebunnya J, Katumba K, et al. Effectiveness and cost-effectiveness of integrating the management of depression into routine HIV Care in Uganda (the HIV+ D trial): A protocol for a cluster-randomised trial. International journal of mental health systems. 2021;15(1):1-11.
6. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. 2012.
7. Ewing JA. Detecting alcoholism: the CAGE questionnaire. Jama. 1984;252(14):1905-7.
8. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. American journal of psychiatry. 1974;131(10):1121-3.
9. Hayes R, Moulton L. Cluster randomised trials. 2009.
10. Patel V, Weiss HA, Chowdhary N, Naik S, Pednekar S, Chatterjee S, et al. Effectiveness of an intervention led by lay health counsellors for depressive and anxiety disorders in primary care in Goa, India (MANAS): a cluster randomised controlled trial. The Lancet. 2010;376(9758):2086-95.
11. Nakku J, Rathod S, Kizza D, Breuer E, Mutyaba K, Baron E, et al. Validity and diagnostic accuracy of the Luganda version of the 9-item and 2-item Patient Health Questionnaire for detecting major depressive disorder in rural Uganda. Global Mental Health. 2016;3.
12. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine. 2001;16(9):606-13.
13. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine. 2006;166(10):1092-7.
14. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research. 2011;20(10):1727-36.
15. Vergunst F, Jenkinson C, Burns T, Anand P, Gray A, Rugkåsa J, et al. Psychometric validation of a multi-dimensional capability instrument for outcome measurement in mental health research (OxCAP-MH). Health and quality of life outcomes. 2017;15(1):1-11.
16. Hooper R, Forbes A, Hemming K, Takeda A, Beresford L. Analysis of cluster randomised trials with an assessment of outcome at baseline. BMJ. 2018;360:k1121.
17. Clifton L, Clifton DA. The correlation between baseline score and post-intervention score, and its implications for statistical analysis. Trials. 2019;20(1):43.
18. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Satariano SA, Jewell N, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology. 2010:467-74.
19. Drechsler J. Multiple imputation of multilevel missing data—Rigor versus simplicity. Journal of Educational and Behavioral Statistics. 2015;40(1):69-95.
20. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med. 2017;377(14):1391-8.
21. Murray EJ, Hernán MA. Adherence adjustment in the Coronary Drug Project: a call for better per-protocol effect estimates in randomized trials. Clinical Trials. 2016;13(4):372-8.

22. Ede V, Okafor M, Kinuthia R, Belay Z, Tewolde T, Alema-Mensah E, et al. An Examination of Perceptions in Integrated Care Practice. Community mental health journal. 2015;51(8):949-61.

Appendix A. Randomization summary

HIV+D randomization summary

MN, 28 November 2020

Below I describe the method for randomizing 40 clinics and hospitals 1:1 by strata into two arms for the HIV+D intervention trial. This randomization was completed by Melissa Neuman on 28 November 2020 using Stata/SE 16.1.

STRATIFICATION

The randomization was stratified into health clinics and hospitals. There are two hospitals among the units for randomization: Masaka Regional Referral Hospital and TASO Entebbe Center Of Excellence

FINAL ALLOCATION TO ARM A/B

Facility code	Facility name	Stratum	Allocation
K1	Bukulula HC IV	Health Centre	Arm A
K3	Kalungu HC III	Health Centre	Arm A
K4	Kyamulibwa HC III	Health Centre	Arm A
K5	Lukaya HC III	Health Centre	Arm A
K7	Kiragga HC III	Health Centre	Arm B
M1	Bukoto HC III	Health Centre	Arm A
M12	Masaka Regional Referral Hospital	Hospital	Arm B
M2	Kyanamukaaka HC IV	Health Centre	Arm B
M3	Kamulegu HC III	Health Centre	Arm B
M4	Bukakata HC III	Health Centre	Arm A
M5	Bukeeri HC III	Health Centre	Arm B
M6	Buwunga HC III	Health Centre	Arm B
M7	Kiyumba HC IV	Health Centre	Arm A
M8	Mpugwe HC III	Health Centre	Arm A
M9	Armoured Brigade HC III	Health Centre	Arm A
W10	Kiziba HC III	Health Centre	Arm A
W12	Mende HC III	Health Centre	Arm B
W13	Namayumba HC IV	Health Centre	Arm A
W14	Nsangi HC III	Health Centre	Arm A
W15	Nakawuka HC III	Health Centre	Arm A
W16	Wakiso Epi Centre HC III	Health Centre	Arm B
W17	Wakiso HC IV	Health Centre	Arm B
W18	Nabutiti HC III	Health Centre	Arm A
W19	Namulonge HC III	Health Centre	Arm A
W2	TASO Entebbe Center Of Excellence	Hospital	Arm A
W21	Buwambo HC IV	Health Centre	Arm B
W22	Ttikalu HC III	Health Centre	Arm A

Facility code	Facility name	Stratum	Allocation
W23	Bweyogerere HC III	Health Centre	Arm B
W24	Kira HC III	Health Centre	Arm B
W25	Kawanda HC III	Health Centre	Arm A
W26	Kasangati HC IV	Health Centre	Arm B
W27	Watubba HC III	Health Centre	Arm B
W28	Nabweru HC III	Health Centre	Arm B
W31	Ndejje HC IV	Health Centre	Arm A
W4	Kajjansi HC IV	Health Centre	Arm B
W5	Luwunga Barracks HC III	Health Centre	Arm B
W6	Kakiri HC III	Health Centre	Arm B
W7	Kasanje HC III	Health Centre	Arm A
W8	Kyengera HC III	Health Centre	Arm B
W9	Busawamanze HC III	Health Centre	Arm B

ALLOCATION TO ACTIVE ARM

I additionally randomized arms A and B to active arm or no. Arm B was randomly allocated to the active arm.

(A do-file has been saved separately and Stata log is pasted below.)

```
 ----------------------------------------------------------------------------------
      name:  <unnamed>
       log:  C:\Users\eidemneu\Filr\My Files\My Documents\HIV_D\outputs\HIV_D_rand
> .txt
  log type:  text
 opened on:  28 Nov 2020, 16:53:06

.
. clear

. set more off

.
. cd "C:\Users\eidemneu\Filr\My Files\My Documents\HIV_D"
C:\Users\eidemneu\Filr\My Files\My Documents\HIV_D

. insheet using "data random - 24 Nov\Copy of Health Facilities for randomization_
> WS v1.1 18 Nov 2020.txt" /// file from Wilber saved as text
>
(9 vars, 40 obs)

. * Recode HF types
.
. // local hf "healthcenter_iii healthcenter_iv district_hospital regional_referra
> l_hospital private_nfp "
. * No district hospitals, so removed from list
.
. local hf "healthcenter_iii healthcenter_iv regional_referral_hospital private_nf
> p "

.
. foreach var of local hf {
  2.                replace `var'="1" if `var'=="*"
  3.                replace `var'="0" if `var'==""
  4.                destring `var', replace
  5. }
(29 real changes made)
(11 real changes made)
healthcenter_iii: all characters numeric; replaced as byte
(9 real changes made)
(31 real changes made)
healthcenter_iv: all characters numeric; replaced as byte
(1 real change made)
(39 real changes made)
regional_referral_hospital: all characters numeric; replaced as byte
(1 real change made)
(39 real changes made)
private_nfp: all characters numeric; replaced as byte

.
. gen stratum=2

. replace stratum=1 if regional_referral==1 | private_nfp==1
(2 real changes made)
```

```
. lab def stratum 1 "Hospital" 2 "Health Centre"

. lab val stratum stratum

. lab var stratum "Randomization strata"

.
. ***** RANDOMIZE *****
.
. gen allocation=0

. lab def allocation 0 "Arm A" 1 "Arm B"

. lab val allocation allocation


.
. * Randomize hospitals - maximum into arm A
. set seed 123456

. gen random=runiform()

. egen rank_random=rank(random) if stratum==1, unique
(38 missing values generated)

. replace allocation=1 if rank_random==1
(1 real change made)

.
. * Randomize clinics - maximum into arm A
. set seed 357913

. capture drop random rank_random

. gen random=runiform()

. egen rank_random=rank(random) if stratum==2, unique
(2 missing values generated)

. replace allocation=1 if rank_random<=19
(19 real changes made)

.
. tab allocation, m

 allocation |      Freq.     Percent        Cum.
------------+-----------------------------------
      Arm A |         20       50.00       50.00
      Arm B |         20       50.00      100.00
------------+-----------------------------------
      Total |         40      100.00

. list facilitycode facilityname stratum allocation, clean noobs

    facil~de                    facilityname         stratum    alloca~n
```

K1	Bukulula HC IV	Health Centre	Arm A
K3	Kalungu HC III	Health Centre	Arm A
K4	Kyamulibwa HC III	Health Centre	Arm A
K5	Lukaya HC III	Health Centre	Arm A
K7	Kiragga HC III	Health Centre	Arm B
M1	Bukoto HC III	Health Centre	Arm A
M12	Masaka Regional Referral Hospital	Hospital	Arm B
M2	Kyanamukaaka HC IV	Health Centre	Arm B
M3	Kamulegu HC III	Health Centre	Arm B
M4	Bukakata HC III	Health Centre	Arm A
M5	Bukeeri HC III	Health Centre	Arm B
M6	Buwunga HC III	Health Centre	Arm B
M7	Kiyumba HC IV	Health Centre	Arm A
M8	Mpugwe HC III	Health Centre	Arm A
M9	Armoured Brigade HC III	Health Centre	Arm A
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W7	Kasanje HC III	Health Centre	Arm A
W8	Kyengera HC III	Health Centre	Arm B
W9	Busawamanze HC III	Health Centre	Arm B

```
.
. clear

.
. * Which arm is which?
.
. set obs 2
number of observations (_N) was 0, now 2

. gen arm="A"

. replace arm="B" if _n==2
(1 real change made)
```

```
.
. set seed 88888888

. gen random=runiform()

. egen rank_random=rank(random)

. gen active_arm=0

. replace active_arm=1 if rank==1
(1 real change made)

. list arm active_arm, clean noobs

    arm   active~m
      A         0
      B         1

.
. clear

. capture log close
```

Appendix B: diagram of CRFs used in HIV+D study