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Major depressive disorder: Longitudinal analysis of impact on clinical and behavioural outcomes in Uganda

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Running header

Impact of depression on HIV outcomes

Abstract

Background: There is still wide variability in HIV disease course and other HIV related outcomes, attributable in part to psychosocial factors such as major depressive disorder (MDD), a subject that has received little attention in sub-Saharan Africa.

Methods: Using a longitudinal cohort of 1099 HIV positive antiretroviral therapy (ART) naïve persons, we investigated the impact of MDD on four HIV related negative outcome domains in Uganda. MDD was assessed using a Diagnostic Statistical Manual IV based tool. Also collected was data on surrogate measures of the HIV related outcome domains. Data

was collected at the three time points of baseline, 6 and 12 months. Multiple regression and discrete time survival models were used to investigate the relationship between MDD and indices of the HIV outcomes.

Results: MDD was a significant predictor of 'missed ART doses' (aOR=4.75, 95% CI, 1.87-12.04, p=0.001), 'time to first visit to healthy facility' (aOR=1.71; 95% CI, 1.07-2.73; p=0.024), 'time to first self-reported risky sexual activity' (aOR=2.11, 95% CI, 1.27-3.49; p=0.004) but not of 'CD4 counts at months 6 and 12' (estimated effect 29.0; 95% CI, -7.8-65.7; p=0.12) and 'time to new WHO stage 3 or 4 clinical event' (aOR=0.52, 95% CI, 0.12-2.20, p=0.37).

Conclusion: MDD significantly impacted three of the four investigated outcome domains. These results by demonstrating the adverse consequences of an untreated mental health disorder (MDD) on HIV related outcomes, further strengthen the need to urgently act on WHO's call to integrate mental health care in general HIV care.

Key Words: Major depressive disorder, HIV outcome measures, ART adherence, risky sexual behaviour, HIV disease progression, health seeking behaviour, Africa

Background

Depressive disorders are estimated to account for 40% of the 183·9 million disability-adjusted life years (DALYs) lost worldwide due to mental and substance use disorders with more than 80% of this non-fatal disease burden occurring in low- and middle-income countries.[1] HIV/AIDS is one of the physical disorders associated with depressive disorders with rates of between 8 to 30% reported in sub-Saharan African studies.[2] Major depressive disorder (MDD) in HIV not only leads to severe psychological distress, it has been implicated in the still wide variability observed in HIV disease course and other related clinical and

behavioural outcomes. In studies largely carried out in the west, MDD has been associated with faster HIV disease progression,[3-5] poor drug adherence,[6-7] poor health seeking behaviour[8] and risky sexual behaviour.[9] Cross-sectional investigation of these associations is often complicated by the bidirectional causal relationships, hence the need for longitudinal study designs.[10] To-date, only two such longitudinal studies have been undertaken in sub-Saharan Africa, with one study showing that MDD negatively impacted HIV disease progression and mortality[11] and the other study showing that MDD negatively impacted risky sexual behaviour.[12]

Additionally, understanding the relationship between MDD and HIV related outcomes in a given socio-cultural context has implications for the design of HIV related clinical trials and for programmatic development in HIV care. On clinical trial design, studies in this area will inform which HIV related outcomes could be used as secondary outcome measures in trials that target depression in HIV in a given socio-cultural context. At the programmatic level, such studies will inform which psychosocial factors in a given socio-cultural context should additionally be targeted to attain maximum impact against a given set of negative HIV related outcomes. In this study, we investigate the impact of MDD on indices of the four HIV related outcomes of HIV disease progression, adherence to HIV medications, health seeking behaviour and risky sexual behaviour using a longitudinal study design in Uganda.

METHODS

Study design and Site

This was a prospective cohort study conducted in adult antiretroviral therapy (ART) naïve persons living with HIV (PLWH) attending at two specialised HIV clinics run by The AIDS Support Organisation (TASO) in Uganda.[13] Data collection was undertaken at three time points: baseline (when participants undertook their first study interview after enrolment into

the study) 6-months after the baseline assessment and 12-months after baseline assessment. Initiation of ART was implemented by TASO independently of the study.

At the time of the study, national treatment guidelines for HIV-infected individuals recommended the initiation of ART at a CD4 cell count of below 250 cells / µl. In addition, individuals initiating ART were required to have identified an appropriate treatment supporter.

Sampling Procedure

The TASO clinic in Entebbe (semi-urban site) has 7,000 active clients of whom about 3,000 are ART naïve while the TASO clinic at Masaka (predominantly rural site) has 6,000 active clients of whom about 2,500 are not on ART. This study aimed to enrol 1100 ART naïve HIV-infected adults from the two clinics. This sample size was chosen to ensure that the baseline prevalence of MDD would be estimated with sufficient precision and would also be sufficient to detect moderate associations between MDD and HIV clinical and behavioural outcomes. To obtain the required sample from the two HIV clinics, a sub-register of all active clients who were not on ART was created. From these sub-registers a random sample of ART naïve patients was recruited from each study clinic using a table of random numbers until a combined total study sample of 1100 was obtained. About 2% of selected patients could not be recruited into this study because of any one of the following reasons: i) they did not meet eligibility criteria; nor ii) were already enrolled in another study nor iii) refused to participate in the study for any other reason.

The inclusion criteria for this study were: i) a person living with HIV/AIDS who was ART naïve and registered with the outpatient clinic at either TASO Entebbe and TASO Masaka clinics; ii) aged at least 18 years old at enrolment; iii) conversant in Luganda, the language in which the study instruments were translated. Exclusion criteria were patients who were too

sick or unable to understand the study instruments, and those who had missed their most recent scheduled clinic visit. Eligible participants were recruited after they had provided written informed consent after explanation of the study objectives and procedures.

Data collection tools

The data collection tools consisted of structured and standardised locally translated psychosocial assessment instruments, most of which have previously been used among persons living with HIV (PLWH) in Uganda by this study group.[14] Study variables from these instruments were categorised as follows: socio-demographic factors: these included study site, sex, age, highest educational attainment, marital status, religion, occupation and socio-economic index (SES index) constructed from commonly available household items in a typical Ugandan households and previously used by this research group;[14] Exposure variable: Current major depressive disorder (MDD) which is the exposure in this study was assessed using the Diagnostic Statistical Manual IV based MDD module of the Mini International Neuropsychiatric Interview (M.I.N.I.-Plus), a tool though never formerly validated in Uganda but has been subject to a formal translation process and used quite extensively.[15] MDD was assessed at each of the three time points of baseline, 6 months and at 12 months. MDD was reported as a binary outcome with respondents reported as either having MDD or not having MDD. A diagnosis of current MDD was made if the respondent within a time period of not less than two weeks, met the following three symptom criteria: i) Criteria 1: must have at least one of the two symptoms (i) or (ii): i) feeling depressed or down, most of the day, nearly every day; ii) had lost interest in most things or much less able to enjoy the things they used to enjoy most of the time; Criteria 2: must have a total of at least five symptoms from the list of (i) to (ix), symptoms (i) and (ii) are described under criteria 1, while symptoms (iii) to (ix) are now described: iii) experienced weight increase or decrease without trying intentionally; iv) had trouble sleeping nearly every night; v) talked or moved

more slowly than normal or were having trouble sitting still almost every day; vi) feeling tired or without energy almost every day; vii) feeling worthless or guilty almost every day; viii) had difficulty concentrating or making decisions almost every day; ix) repeatedly considered hurting yourself, feeling suicidal, or wishing that you were dead, or attempted suicide or had a suicide plan; Criteria 3: the above listed symptoms should cause significant problems at home, at work, socially, or at school or in some other important way.

Indices of HIV related outcome measures: data on these indices was collected at each of the three data collection time points of baseline, 6 months and 12 months. These indices were grouped into the following four domains, i) HIV disease progression (CD4 counts, WHO Clinical Staging criteria[16]); ii) health seeking behaviour (number of visits to health facilities in last month[14]); iii) adherence to HIV medications (three day antiretroviral therapy pill count recall[14]); and iv) risky sexual behaviour (assessed by inquiring about five risky sexual behaviours that have been associated with HIV transmission in the Ugandan cultural context,[17] these questions were, 'In the last month, have you: i) had sex with anyone other than your regular partner?; ii) have you had sex in exchange for gifts/money?; iii) have you had forced sex including rape?; iv) have you had sex with someone much older/younger than you?; v) have you had sex with someone you had just met?)'.

Statistical Analysis

The impact of MDD on the four HIV-related outcome domains was investigated using five outcome variables, as described below:

HIV disease progression domain

i) CD4 count at visit 2 (6 months) and visit 3 (12 months) was one of the outcome variables used to measure the domain HIV disease progression. The analysis used a "long" data set

which included for each participant the CD4 cell count at month 6 and month 12. The primary exposure, MDD, was lagged i.e. MDD at baseline was used as the exposure variable for CD4 count at month 6, while MDD at month 6 was used as the exposure for CD4 count at month 12. The reason for lagging MDD was that the CD4 count at a particular visit was deemed to reflect everything that happened in the previous 6 month period. Multiple linear regression models were fitted with the use of robust standard errors to account for the correlation between CD4 counts within participants. It was felt that two observations per subject was too few to fit linear mixed models for repeated measurements. The analysis adjusted for study site, sex, age, visit (i.e. month 6 or month 12) and baseline CD4 cell count as explanatory variables. Participants who initiated ART between baseline and month 6 were excluded, while participants who initiated ART between month 6 and month12 were included at month 6 but excluded at month 12. The measure of effect for CD4 count is the difference in CD4 cell count (cells / µl) between participants with MDD (at the previous visit) and those without MDD.

ii) Having experienced a WHO stage 3 or 4 event at month 6 or month 12 was also used to measure the domain HIV disease progression. The time to the first WHO stage 3 or 4 event was analysed using discrete time survival models.[18-19] Discrete-time survival models were used to investigate the time (6 months or 12 months) to the first WHO stage 3 or 4 event. In practice this is done by fitting logistic regression models, so although the derivation is based on the hazard (risk of an event at the given visit), the parameters of the model can be interpreted as odds ratios. The primary exposure, MDD, was lagged i.e. MDD at baseline was used as the exposure variable for a WHO stage 3 or 4 event at month 6, while MDD at month 6 was used as the exposure for a WHO stage 3 or 4 event at month 12. The analysis adjusted for study site, sex, age, visit (i.e. month 6 or month 12) and baseline CD4 cell count as explanatory variables.

Participants who initiated ART before month 6 were excluded, while those who initiated ART between month 6 and month 12 were included at month 6 but excluded at month 12. Participants who had already experienced a WHO stage 3 or 4 event at baseline were also excluded from the analysis. The measure of effect is the (adjusted) odds ratio for a WHO stage 3 or 4 event for participants with MDD (at the previous visit) compared to those without MDD.

Adherence to HIV medications domain

iii) Having missed at least one dose of ART medications in the three days prior to the interview was used as a measure for the domain on adherence to HIV medication. Missing at least one dose of ART at month 6 and month 12 was analysed by fitting a multiple logistic regression model to a "long" data set with up to 2 observations per participant; robust standard errors were used to account for the correlation of responses within participants. In this case the primary exposure (MDD) was not lagged, since the MDD was evaluated over the two weeks prior to the visit and missing at least one dose of ART was evaluated over the three days prior to the visit, so we assumed that the exposure (MDD) preceded the outcome (missing at least one dose of ART). The analysis adjusted for study site, sex, age, visit (i.e. month 6 or month 12) and baseline CD4 cell count as explanatory variables. The analysis was restricted to participants who initiated ART between baseline and month 6 (who were included at month 6 and month 12) and participants who initiated ART between month 6 and month 12 (who were included at month 12 only). The measure of effect is the (adjusted) odds ratio for missing at least one dose of ART for participants with MDD compared to those without MDD.

Health seeking behaviour domain

(iv) The time to the first visit to a health facility was used as a measure of health seeking behaviour and was analysed using discrete time survival models. The primary exposure, MDD, was lagged i.e. MDD at baseline was used as the exposure variable for a visit to a health facility at month 6, while MDD at month 6 was used as the exposure variable for a visit to a health facility at month 12. The analysis adjusted for study site, sex, age, visit (i.e. month 6 or month 12) and baseline CD4 cell count as explanatory variables. Participants who had their first visit to a health facility at baseline were excluded from the analysis, while those who visited a health facility between month 6 and month 12 were included at month 6 but excluded at month 12. The measure of effect is the (adjusted) odds ratio for a visit to a health facility for participants with MDD (at the previous visit) compared to those without MDD.

Risky sexual behaviour domain

v) Having engaged in risky sexual behaviour (as measured by at least one affirmative answer to the five questions on sexual behaviour) was analysed using discrete time survival models. The primary exposure (MDD) was lagged. The analysis adjusted for study site, sex, age, visit and baseline CD4 count as explanatory variables. Participants who had engaged in risky sexual behaviour at baseline were excluded from the analysis, while those who engaged in risky sexual behaviour at month 6 were excluded at month 12. The measure of effect is the (adjusted) odds ratio for risky sexual behaviour for participants with MDD (at the previous visit) compared to those without MDD.

We did not adjust for multiple significance testing. While this increases the chance of type I errors, the aim of the analysis was to identify potentially detrimental consequences of MDD which can be seen as analogous to safety analysis in drug trials in which the aim is to identify

potential risks caused by the investigational drug, in which case adjusting for multiplicity is not recommended.[20]

Ethical Considerations

The study obtained ethical approval from the Uganda Virus Research Institute's Science and Ethics Committee and the Uganda National Council of Science and Technology. Study participants were invited to consent and participate in this study by trained psychiatric nurses after being provided with adequate information about the study. Respondents found to have significant psychiatric problems were referred to psychiatric departments nearest to their study sites for further assessment and management.

RESULTS

Overall retention in the study at one year was high, with 1,041 (94.7%) of participants seen at month 12. Of the 1099 participants assessed at baseline, 67 (6.2%) were lost to follow-up by 12 months, of whom 18 were confirmed to have died during the course of this study, the majority due to non HIV related causes. None of the factors of study site, sex, marital status and baseline MDD were associated with loss to follow-up. In this study, missing data of not more than 1% was recorded on the variables educational status, marital status, current MDD, visits to health facilities in the past month and any risky sexual activity. It was only on the variable WHO stage that missing data of 2.8% was recorded at the 12 months data collection time point (see Table 1 for details).

Socio-demographic factors, psychosocial exposure and HIV related outcomes

insert Table 1

A summary of socio-demographic data, psychosocial exposure variable and clinical and behavioural outcomes are given in Table 1. A detailed description of the characteristics of this study population can be found in earlier publications.[2, 21] The number of participants at the two study sites was similar throughout the three reporting periods (baseline, 6 months and 12 months). Overall just over three-quarter of participants were female and the mean age overall was 35 years. Only 296 (27%) of participants had secondary or higher education. About half of the participants were currently married, with less than 104 (10%) having never been married. The proportion of respondents with a current episode of major depressive disorder (MDD) decreased from 155 (14%) at baseline to 59 (5.6%) at month 6 and to a further 44 (4.2%) at month 12.

In this study, CD4 cell counts showed large variability, both between participants and between periods within participants. The CD4 count increased over time; this increase can be partly explained by the fact that participants who started ART, and who had the lowest CD4 counts, were excluded from the subsequent analysis of CD4 counts. The baseline CD4 counts were based on 1099 participants, while at month 6 the CD4 counts were based on 694 participants who had not yet started ART and at month 12 the CD4 counts were based on 547 participants who had not yet started ART. Few participants experienced a new WHO stage 3 or 4 event, 6% at baseline, of those without a baseline event, 3.4% at month 6 and of the remainder 4.6% at month 12.

Associations between the MDD and HIV clinical and behavioural outcomes

Given below are the results of fitting models to find associations between MDD and HIV related clinical and behavioural outcomes.

insert Table 2

Model for CD4 counts

The analysis of the CD4 count by fitting a linear regression model, with the use of robust variance estimation to adjust for the within-subject correlation at month 6 and month 12, was based on 694 participants at month 6 and 547 participants at month 12; participants were excluded from this analysis if they had initiated ART prior to the visit concerned. The results of fitting the linear regression model with robust variance estimators are summarised in Table 2a. MDD was not significantly associated with the CD4 count at the follow-up visits, adjusting for study site, sex, age and baseline CD4 count. The estimated effect showed that participants with MDD had higher CD4 counts on average, but the difference was not statistically significant (estimated effect 29.0; 95% CI, -7.8-65.7; p=0.12).

Model for time to first new WHO stage 3 or 4 event

The analysis of the time to the first new WHO stage 3 or 4 event using a discrete time survival model was based on 706 participants, with 333 participants excluded due to initiating ART and 28 participants excluded as they had experienced a WHO stage 3 or 4 event at baseline. In total 24 participants experienced a WHO stage 3 or 4 event at month 6 and a further 25 participants experienced a WHO stage 3 or 4 event at month 12. The results of fitting the discrete time survival model are summarised in Table 2b. MDD was not

significantly associated with the odds of experiencing a WHO stage 3 or 4 event, adjusting for study site, sex, age and baseline CD4 count (aOR =0.52; 95% CI, 0.12-2.20; p=0.37).

Model for having missed a dose of ART

The analysis of having missed at least one dose of ART was based on 468 participants of whom 333 had initiated ART by month 6. At month 6, 30/333 participants missed at least one dose of ART in the 3 days prior to the visit, while at month 12, 31/468 participants missed at least one dose of ART. The results of fitting a logistic regression model with robust variance estimators are summarised in Table 2c. Adjusting for study site, sex, age and baseline CD4 count, the odds of having missed at least one dose of ART were 4.75 times as high for participants with MDD compared to those without MDD (aOR=4.75; 95% CI, 1.87-12.04); p=0.001).

Model for having visited a health facility

The analysis of the time to the first visit to a health facility using a discrete time survival model was based on 763 participants; the 309 participants who had visited a health facility at baseline were excluded from the analysis. In total 146 participants visited a health facility in the month before visit 2 (month 6) and a further 77 participants visited a health facility in the month before visit 3 (month 12). The results of fitting a discrete time survival model are summarised in Table 2d. Adjusting for study site, sex, age and baseline CD4 count, the odds of having undertaken a visit to the health facility were 1.71 times as high for participants with MDD (at the previous visit) compared to those without MDD (aOR=1.71; 95% CI, 1.07-2.73; p=0.024).

Model for any risky sexual behaviour

The analysis of the time to the first self-reported risky sexual behaviour using a discrete time survival model was based on 906 participants; 147 participants were excluded as they reported having engaged in risky sexual behaviour at baseline, while 20 participants had missing responses to all five questions at month 6 and 36 participants had missing responses to all five questions at month 12. In total 74 participants reported in having engaged in risky sexual behaviour at month 6 and a further 67 reported having engaged in risky sexual behaviour at month 12. The results of fitting a discrete time survival model are summarised in Table 2e. Adjusting for study site, sex, age and baseline CD4 count, the odds of having engaged in risky sexual behaviour were 2.11 times as high for participants with MDD (at the previous visit) compared to those without MDD (aOR=2.11; 95% CI, 1.27-3.49; P=0.004).

DISCUSSION

This to our knowledge is only the third paper from sub-Saharan Africa that has investigated the association between MDD and HIV related negative outcomes using a prospective study design to control for possible bidirectionality.[10] While each of the two earlier studies only looked at the relationship between MDD and one HIV related outcome,[11-12] this study investigated the relationship between MDD and indices of the four HIV related outcome domains of HIV disease progression, adherence to HIV medications, health seeking behaviour and risky sexual behaviour.

Two indices were used to assess HIV disease progression in this study, namely, CD4 counts at 6 and 12 months and time to the first new WHO stage 3 or 4 event. In this study we found no evidence that MDD at the previous visit was associated with either of these two indices used to assess for HIV disease progression. In the literature there are conflicting results on the association between MDD and HIV disease progression with some systematic reviews and

meta-analyses reporting a significant association[4] while others do not report such a finding.[22] Possible explanations for these conflicting results include the complexity of the relationship between neuropsychiatric disorders such as MDD and the immune system in HIV/AIDS[23-24] and methodological issues including differences in study design and choice of HIV disease progression indicators[4] and the high variability of some indices used as a surrogate measure of HIV disease progression.[24] Indeed, the relationship between MDD and CD4 counts in this study could have been confounded by the wide variability shown by CD4 counts both between subjects and between time periods within subjects.

In this study we found that MDD at the current visit was associated with nearly a five-fold increase in the odds of missing at least one dose of ART in the previous three days. While we feel this was a fairly robust finding, it is important to note that there were smaller numbers on ART compared to the cohort as a whole. In line with these findings, two previous systematic reviews have reported that depression negatively impacted ART adherence.[6,25] On health seeking behaviour, our findings were that having a previous episode of MDD was associated with a nearly two-fold increased risk of visiting a health facility. While previous studies have reported MDD as a predictor of poor access to general HIV care services,[8] a multi-site European study reported increased utilisation of psychiatric services by individuals with MDD in the community.[26] The increased utilisation of HIV care services that was associated MDD in this study may have been a 'cry for help' from persons experiencing psychological distress whose needs were not being met by an HIV care system that is not yet responsive to the mental health needs of persons living with HIV. We did not control for distance between the respondent's home and the HIV clinic, a variable that could have confounded the above relationship.

We observed that MDD was associated with a two-fold increased risk of engaging in risky sexual behaviour. Both Seth and colleagues (2011)[9] among female African American adolescents in the United States of America and Nduna and colleagues (2010)[12] among young adults in South Africa have reported MDD as a significant predictor of risky sexual behaviour.

In conclusion, this study has demonstrated that MDD significantly impacted the HIV related outcome domains of adherence to HIV medications, health seeking behaviour and risky sexual behaviour but not of HIV disease progression. These results add further weight to the recent recommendation by the WHO to integrate mental health into HIV care services[27] by demonstrating the adverse consequences of an untreated mental health disorder (MDD) on HIV related clinical and behavioural outcomes. Additionally, these results support an observation made by Collins et al (2006) who in a systematic review on the relevance of mental health to HIV/AIDS care and treatment programs in developing countries noted that behavioural factors including mental health disorders are likely to be a major determinant in ART roll.[28] In response to this observation, Collins et al (2006) then called for methodologically sound studies, such as this one, that among others describe the mental health-related predictors of ART adherence. Finally, these results suggest that in the sub-Saharan African setting of Uganda, psychosocial factors such as MDD should among others be targeted in the design of interventions to address the HIV outcomes of adherence to HIV medications, health seeking behaviour and risky sexual behaviour. There is however need for more studies to further validate these findings in this socio-cultural context.

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Table 1: Socio-demographics, psychosocial exposures and HIV related outcomes of the study population by data collection time period

Factor	Level	Baseline	Month 6	Month 12
Overall		1099	1059	1041
Socio-demographics				
Study Site	Entebbe	542 (49.3%)	520 (49.1%)	509 (48.9%)
	Masaka	557 (50.7%)	539 (50.9%)	532 (51.1%)
Sex	Male	252 (22.9%)	243 (23.0%)	238 (22.9%)
	Female	847 (77.1%)	816 (77.0%)	803 (77.1%)
Age	Mean (s.d.)	35.1 (9.3)	35.1 (9.3)	35.1 (9.1)
	Median (IQR)	34 (28 – 41)	34 (28 – 41)	34 (28 – 41)
Age (grouped)	18 – 29	339 (30.8%)	321 (30.3%)	316 (30.4%)
	30 – 34	252 (22.9%)	248 (23.4%)	244 (23.4%)
	35 – 39	197 (17.9%)	188 (17.8%)	185 (17.8%)
	40 – 49	225 (20.5%)	218 (20.6%)	216 (20.8%)
	>=50	86 (7.8%)	84 (7.9%)	80 (7.7%)
Education Status	None	120 (10.9%)	113 (10.7%)	113 (10.8%)
	Primary	680 (61.9%)	654 (61.8%)	641 (61.6%)
	Secondary or more	296 (26.9%)	289 (27.3%)	284 (27.3%)
	Missing	3 (0.3%)	3 (0.3%)	3 (0.3%)
Marital Status	Currently married	563 (51.2%)	540 (51.0%)	533 (51.2%)
	Widowed	163 (14.8%)	157 (14.8%)	158 (15.2%)
	Separated / divorced	267 (24.3%)	261 (24.6%)	254 (24.4%)
	Single	104 (9.5%)	99 (9.4%)	94 (9.0%)
	Missing	2 (0.2%)	2 (0.2%)	2 (0.2%)
Religion	Catholic	586 (53.3%)	566 (53.4%)	562 (54.0%)
	Protestant	237 (21.6%)	228 (21.5%)	224 (21.5%)
	Muslim	163 (14.8%)	158 (14.9%)	152 (14.6%)
	Seventh Day	16 (1.5%)	16 (1.5%)	14 (1.3%)
	Born Again	93 (8.5%)	87 (8.2%)	85 (8.2%)
	Other	4 (0.4%)	4 (0.4%)	4 (0.4%)
Occupation	Farmer / Fishing	324 (29.5%)	321 (30.3%)	310 (29.8%)
	Professional / clerical	43 (3.9%)	42 (4.0%)	42 (4.0%)
	Trader / Artisan / transport	396 (36.0%)	386 (36.4%)	383 (36.8%)
	Unemployed / Retired / housewife	139 (12.6%)	126 (11.9%)	126 (12.1%)
	Student / other	187 (17.0%)	174 (16.4%)	172 (16.5%)
		10 (0.9%)	10 (0.9%)	8 (0.8%)
SES index	Mean (s.d.)	15.1 (3.6)	15.1 (3.6)	15.1 (3.6)
	Median (IQR)	15 (13 – 17)	15 (13 – 17)	15 (13 – 17)
Psychosocial exposures				
Current MDD	No	944 (85.9%)	991 (93.6%)	987 (94.8%)
	Yes	155 (14.1%)	59 (5.6%)	44 (4.2%)
	Missing	0	9 (0.8%)	10 (1.0%)
HIV related outcomes				
CD4 count	Mean (s.d.)	516.2 (267.6)	560.6 (235.4)	600.6 (233.4)
	Median (IQR)	471 (352 ; 665)	517 (407 ; 687)	556 (435 ; 711)
	Geometric mean (95% C.I.)	430.7 (412 ; 450)	514.6 (498 ; 532)	516.1 (497 ; 537)
WHO stage	I	533 (48.5%)	308 (45.4%)	233 (43.3%)
	II	500 (45.5%)	347 (51.2%)	265 (49.3%)
	III / IV	66 (6.0%)	23 (3.4%)	25 (4.6%)

	Missing	0	0	15 (2.8%)
Missed a dose of ART in past three days	No		289 (86.8%)	390 (83.3%)
	Yes		30 (9.0%)	31 (6.6%)
	N/A		14 (4.2%)	47 (10.0%)
Visits to health facility in past month	None	781 (71.1%)	603 (80.1%)	507 (86.7%)
	Once	146 (13.3%)	70 (9.3%)	47 (8.0%)
	Twice	85 (7.7%)	45 (6.0%)	18 (3.1%)
	Three or more	86 (7.8%)	31 (4.1%)	10 (1.7%)
	Missing	1 (0.1%)	4 (0.5%)	3 (0.5%)
Any Risky sexual activity	No	950 (86.4%)	832 (91.0%)	737 (90.9%)
	Yes	149 (13.6%)	74 (8.1%)	66 (8.1%)
	Missing	0	8 (0.9%)	8 (1.0%)

Table 2: Results of fitting models to outcomes associated with MDD

Table 2 a) Multiple linear regression with robust variance estimation for CD4 counts

Factor	Level	Effect (Robust 95% c.i.)	P-value
Study SIte	Entebbe	0 (Reference)	<0.001
	Masaka	53.8 (28.3 ; 79.4)	
Sex	Male	0 (Reference)	0.024
	Female	33.8 (4.5 ; 63.1)	
Age	Per 10 year increase	-9.5 (-23.0 ; 4.1)	0.17
Visit	Visit 2 (Month 6)	0 (Reference)	<0.001
	Visit 3 (Month 12)	23.6 (6.4 ; 40.9)	
Baseline CD4 count	Per unit increase	0.56 (0.49 ; 0.63)	<0.001
MDD (lagged)	No	0 (Reference)	0.12
	Yes	29.0 (-7.8 ; 65.7)	

Table 2 b) Discrete Time Survival model for time to WHO stage 3 or 4 event

Factor	Level	Adjusted Odds Ratio (95% c.i.)	P-value
Study SIte	Entebbe	1 (Reference)	<0.001
	Masaka	0.30 (0.16 ; 0.57)	
Sex	Male	0 (Reference)	0.68
	Female	1.17 (0.56 ; 2.47)	
Age	Per 10 year increase	1.16 (0.85 ; 1.58)	0.35
Visit	Visit 2 (Month 6)	1(Reference)	0.26
	Visit 3 (Month 12)	1.40 (0.78 ; 2.51)	
Baseline CD4 count	Per 100 cell / µl increase	1.004 (0.89 ; 1.13)	0.95
MDD (lagged)	No	1 (Reference)	0.12
	Yes	0.52 (0.12 ; 2.20)	

Table 2 c) Logistic Regression model with robust variance for missing ART

Factor	Level	Adjusted Odds Ratio (robust 95% c.i.)	P-value
Study SIte	Entebbe	1 (Reference)	0.007
	Masaka	0.36 (0.17 ; 0.76)	
Sex	Male	0 (Reference)	0.52
	Female	0.83 (0.47 ; 1.47)	
Age	Per 10 year increase	0.98 (0.72 ; 1.33)	0.90
Visit	Visit 2 (Month 6)	1(Reference)	0.38
	Visit 3 (Month 12)	0.79 (0.48 ; 1.32)	
Baseline CD4 count	Per 100 cell / µl increase	0.94 (0.79 ; 1.11)	0.45
MDD (lagged)	No	1 (Reference)	0.001
	Yes	4.75 (1.87 ; 12.04)	

Table 2 d) Discrete Time Survival model for time to visit to health facility

Factor	Level	Adjusted Odds Ratio (95% c.i.)	P-value
Study SIte	Entebbe	1 (Reference)	<0.001
	Masaka	3.23 (2.33 ; 4.49)	
Sex	Male	0 (Reference)	0.23
	Female	1.26 (0.86 ; 1.85)	
Age	Per 10 year increase	1.02 (0.86 ; 1.20)	0.82
Visit	Visit 2 (Month 6)	1(Reference)	0.015
	Visit 3 (Month 12)	0.68 (0.49 ; 0.93)	
Baseline CD4 count	Per 100 cell / µl increase	0.97 (0.91 ; 1.02)	0.23
MDD (lagged)	No	1 (Reference)	0.024
	Yes	1.71 (1.07 ; 2.73)	

Table 2 e) Discrete Time Survival model for time to first risky sexual behaviour

Factor	Level	Adjusted Odds Ratio (95% c.i.)	P-value
Study SIte	Entebbe	1 (Reference)	0.25
	Masaka	0.81 (0.56 ; 1.16)	
Sex	Male	0 (Reference)	0.003
	Female	0.55 (0.37 ; 0.81)	
Age	Per 10 year increase	0.71 (0.57 ; 0.88)	0.002
Visit	Visit 2 (Month 6)	1(Reference)	0.64
	Visit 3 (Month 12)	1.09 (0.76 ; 1.55)	
Baseline CD4 count	Per 100 cell / µl increase	0.98 (0.92 ; 1.05)	0.61
MDD (lagged)	No	1 (Reference)	0.004
	Yes	2.11 (1.2 7; 3.49)	