Major Depressive Disorder: Longitudinal Analysis of Impact on Clinical and Behavioral Outcomes in Uganda

Eugene Kinyanda, PhD,†‡ Jonathan Levin, PhD,§ Noeline Nakasujja, PhD,† Harriet Birabwa, MMed,‖ Juliet Nakku, MMed,‖ Richard Mpango, MSc,* Heiner Grosskurth, PhD,‡ Soraya Seedat, PhD,¶ Ricardo Araya, PhD,# Maryam Shahmanesh, FRCP,** and Vikram Patel, PhD††*

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–naive persons, we investigated the impact of MDD on 4 HIV-related negative outcome domains in Uganda. MDD was assessed using a Diagnostic Statistical Manual IV–based tool. Also collected were data on surrogate measures of the HIV-related outcome domains. Data were collected at the 3 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 antiretroviral therapy doses" [adjusted odds ratio (aOR) = 4.75, 95% confidence interval (CI): 1.87 to 12.04, $P = 0.001$], "time to first visit to healthy facility" (aOR = 1.71; 95% CI: 1.07 to 2.73; $P = 0.024$), "time to first self-reported risky sexual activity" (aOR = 2.11, 95% CI: 1.27 to 3.49; $P = 0.004$) but not of "CD4 counts at months 6 and 12" (estimated effect 29.0; 95% CI: −7.8 to 65.7; $P = 0.12$), and "time to new WHO stage 3 or 4 clinical event" (aOR = 0.52, 95% CI: 0.12 to 2.20, $P = 0.37$).

Conclusions: MDD significantly impacted 3 of the 4 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 behavior, HIV disease progression, health-seeking behavior, Africa

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BACKGROUND

Depressive disorders are estimated to account for 40% of the 183·9 million disability-adjusted life years lost worldwide due to mental and substance use disorders with more than 80% of this nonfatal 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% and 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 behavioral outcomes. In studies largely performed in the west, MDD has been associated with faster HIV disease progression,[3–5] poor drug adherence,[6,7] poor health-seeking behavior,[8] and risky sexual behavior.[9] Cross-sectional investigation of these associations is often complicated by the bidirectional causal relationships and hence the need for longitudinal study designs.[10] To date, only 2 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 behavior.[12]

In addition, understanding the relationship between MDD- and HIV-related outcomes in a given sociocultural 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 sociocultural context. At the programmatic level, such studies

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From the *Mental Health Project, MRC/UVRI Uganda Research Unit on AIDS/Senior Wellcome Trust Fellowship, Entebbe, Uganda; †Department of Psychiatry, Makerere College of Health Sciences, Kampala, Uganda; ‡Department of Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; §School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ‖Butabika National Psychiatric Referral Hospital, Kampala, Uganda; ¶Department of Psychiatry, Stellenbousch University, Cape Town, South Africa; #Health Service and Population Research, Centre for Global Mental Health and Primary Care Research, King's College, London, United Kingdom; **Central and North West London NHS Foundation Trust, London, United Kingdom; and ††Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA.

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Correspondence to: Eugene Kinyanda, PhD, Mental Health Project, MRC/UVRI Uganda Research Unit on AIDS, Plot 51-59 Nakiwogo Street, P.O. Box 49 Entebbe, Uganda (e-mail: Eugene.Kinyanda@mrcuganda.org).

will inform which psychosocial factors in a given sociocultural 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 4 HIV-related outcomes of HIV disease progression, adherence to HIV medications, health-seeking behavior, and risky sexual behavior using a longitudinal study design in Uganda.

METHODS

Study Design and Site

This was a prospective cohort study conducted in adult antiretroviral therapy (ART)–naive persons living with HIV (PLWH) attending at 2 specialized HIV clinics run by The AIDS Support Organization (TASO) in Uganda.[13] Data collection was undertaken at 3 time points: baseline (when participants undertook their first study interview after enrollment 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 7000 active clients of whom about 3000 are ART naïve, whereas the TASO clinic at Masaka (predominantly rural site) has 6000 active clients of whom about 2500 are not on ART. This study aimed to enroll 1100 ART-naïve HIV-infected adults from the 2 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 behavioral outcomes. To obtain the required sample from the 2 HIV clinics, a subregister of all active clients who were not on ART was created. From these subregisters, 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: (1) they did not meet eligibility criteria; nor (2) were already enrolled in another study nor (3) refused to participate in the study for any other reason.

The inclusion criteria for this study were as follows: (1) a person living with HIV/AIDS who was ART naïve and registered with the outpatient clinic at either TASO Entebbe and TASO Masaka clinics; (2) aged at least 18 years old at enrollment; and (3) 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 standardized locally translated psychosocial assessment instruments, most of which have previously been used among PLWH in Uganda by this study group.[14] Study variables from these instruments were categorized as follows: sociodemographic factors: These included study site, sex, age, highest educational attainment, marital status, religion, occupation, and socioeconomic index constructed from commonly available household items in a typical Ugandan households and previously used by this research group[14]; exposure variable: Current 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 although 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 3 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 2 weeks met the following 3 symptom criteria: Criteria 1*:* must have at least one of the 2 symptoms (1) or (2): (1) feeling depressed or down, most of the day, nearly every day; (2) 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 5 symptoms from the list of (1) to (9), symptoms (1) and (2) are described under criteria 1, whereas symptoms (3) to (9) are now described: (3) experienced weight increase or decrease without trying intentionally; (4) had trouble sleeping nearly every night; (5) talked or moved more slowly than normal or were having trouble sitting still almost every day; (6) feeling tired or without energy almost every day; (7) feeling worthless or guilty almost every day; (8) had difficulty concentrating or making decisions almost every day; (9) 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 were collected at each of the 3 data collection time points of baseline, 6 months, and 12 months. These indices were grouped into the following 4 domains, (1) HIV disease progression (CD4 counts, WHO Clinical Staging criteria[16]); (2) health-seeking behavior (number of visits to health facilities in last month[14]); (3) adherence to HIV medications (3-day ART pill count recall[14]); and (4) risky sexual behavior (assessed by inquiring about 5 risky sexual behaviors that have been associated with HIV transmission in the Ugandan cultural context,[17] these questions were, "In the last month, have you: *(1) had sex with anyone other than your regular partner?; (2) have you had sex in exchange for gifts/money?; (3) have you had forced sex including rape?; (4) have you*

had sex with someone much older/younger than you?; (5) have you had sex with someone you had just met?)."

Statistical Analysis

The impact of MDD on the 4 HIV-related outcome domains was investigated using 5 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, that is, MDD at baseline was used as the exposure variable for CD4 count at month 6, whereas 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 2 observations per subject were too few to fit linear mixed models for repeated measurements. The analysis adjusted for study site, sex, age, visit (ie, month 6 or month 12), and baseline CD4 cell count as explanatory variables. Participants who initiated ART between baseline and month 6 were excluded, whereas participants who initiated ART between month 6 and month 12 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 analyzed 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 performed 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, that is, MDD at baseline was used as the exposure variable for a WHO stage 3 or 4 event at month 6, whereas 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 (ie, month 6 or month 12), and baseline CD4 cell count as explanatory variables. Participants who initiated ART before month 6 were excluded, whereas 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 with those without MDD.

Adherence to HIV Medications Domain

iii) Having missed at least one dose of ART medications in the 3 days before 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 analyzed 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 2 weeks before the visit and missing at least one dose of ART was evaluated over the 3 days before 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 (ie, 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 with those without MDD.

Health-Seeking Behavior Domain

(iv) The time to the first visit to a health facility was used as a measure of health-seeking behavior and was analyzed using discrete time survival models. The primary exposure, MDD, was lagged, that is, MDD at baseline was used as the exposure variable for a visit to a health facility at month 6, whereas 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 (ie, 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, whereas 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 with those without MDD.

Risky Sexual Behavior Domain

v) Having engaged in risky sexual behavior (as measured by at least one affirmative answer to the 5 questions on sexual behavior) was analyzed 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 behavior at baseline were excluded from the analysis, whereas those who engaged in risky sexual behavior at month 6 were excluded at month 12. The measure of effect is the (adjusted) odds ratio for risky sexual behavior for participants with MDD (at the previous visit) compared with those without MDD.

We did not adjust for multiple significance testing. Although 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

TABLE 1. Sociodemographics, 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
Sociodemographics				
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 (SD)	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	139 (12.6%)	126 (11.9%)	126 (12.1%)
	housewife	187 (17.0%)	174 (16.4%)	172 (16.5%)
	Student/other	10 (0.9%)	10 (0.9%)	8 (0.8%)
SES index	Mean (SD)	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 (SD)	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% CI)	430.7 (412 to 450)	514.6 (498 to 532)	516.1 (497 to 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 3 days	No		289 (86.8%)	390 (83.3%)
	Yes		30 (9.0%)	31 (6.6%)
	N/A		14 (4.2%)	47 (10.0%)

(*continued on next page*)

TABLE 1. (*Continued*) Sociodemographics, Psychosocial Exposures, and HIV-Related Outcomes of the Study Population by Data Collection Time Period

Factor	Level	Baseline	Month 6	Month 12
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%)

IQR, interquartile range; SES, socioeconomic.

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 1041 (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% were 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% were recorded at the 12-month data collection time point (Table 1 for details).

Sociodemographic Factors, Psychosocial Exposure, and HIV-Related Outcomes

A summary of sociodemographic data, psychosocial exposure variable, and clinical and behavioral 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 2 study sites was similar throughout the 3 reporting periods (baseline, 6 months, and 12 months). Overall, just over three-quarter of participants were women 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 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, whereas 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 Behavioral Outcomes

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

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 before the visit concerned. The results of fitting the linear regression model with robust variance estimators are summarized in Table 2. 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

TABLE 2. Results of Fitting Models to Outcomes Associated With MDD: Multiple Linear Regression With Robust Variance Estimation for CD4 Counts

Factor	Level	Effect (Robust 95% CI)	*P*
Study site	Entebbe	0 (reference)	<0.001
	Masaka	53.8 (28.3 to 79.4)	
Sex	Male	0 (reference)	0.024
	Female	33.8 (4.5 to 63.1)	
Age	Per 10-year increase	−9.5 (−23.0 to 4.1)	0.17
Visit	Visit 2 (month 6)	0 (reference)	<0.001
	Visit 3 (month 12)	23.6 (6.4 to 40.9)	
Baseline CD4 count	Per unit increase	0.56 (0.49 to 0.63)	<0.001
MDD (lagged)	No	0 (reference)	0.12
	Yes	29.0 (−7.8 to 65.7)	

was not statistically significant (estimated effect 29.0; 95% CI: −7.8 to 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 because of 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 summarized in Table 3. 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 [adjusted odds ratio (aOR) = 0.52; 95% confidence interval (CI): 0.12 to 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 before the visit, whereas 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 summarized in Table 4. 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 with those without MDD (aOR = 4.75; 95% CI: 1.87 to 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 summarized in Table 5. 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 with those without MDD (aOR = 1.71; 95% CI: 1.07 to 2.73; $P = 0.024$).

Model for Any Risky Sexual Behavior

The analysis of the time to the first self-reported risky sexual behavior using a discrete time survival model was based on 906 participants; 147 participants were excluded as they reported having engaged in risky sexual behavior at baseline, whereas 20 participants had missing responses to all 5 questions at month 6 and 36 participants had missing responses to all 5 questions at month 12. In total, 74 participants reported in having engaged in risky sexual behavior at month 6 and a further 67 reported having engaged

TABLE 3. Results of Fitting Models to Outcomes Associated With MDD: Discrete Time Survival Model for Time to WHO Stage 3 or 4 Event

Factor	Level	Adjusted Odds Ratio (95% CI)	*P*
Study site	Entebbe	1 (reference)	<0.001
	Masaka	0.30 (0.16 to 0.57)	
Sex	Male	0 (reference)	0.68
	Female	1.17 (0.56 to 2.47)	
Age	Per 10-year increase	1.16 (0.85 to 1.58)	0.35
Visit	Visit 2 (month 6)	1 (reference)	0.26
	Visit 3 (month 12)	1.40 (0.78 to 2.51)	
Baseline CD4 count	Per 100-cell/μL increase	1.004 (0.89 to 1.13)	0.95
MDD (lagged)	No	1 (reference)	0.12
	Yes	0.52 (0.12 to 2.20)	

TABLE 4. Results of Fitting Models to Outcomes Associated With MDD: Logistic Regression Model With Robust Variance for Missing ART

Factor	Level	Adjusted Odds Ratio (Robust 95% CI)	*P*
Study site	Entebbe	1 (reference)	0.007
	Masaka	0.36 (0.17 to 0.76)	
Sex	Male	0 (reference)	0.52
	Female	0.83 (0.47 to 1.47)	
Age	Per 10-year increase	0.98 (0.72 to 1.33)	0.90
Visit	Visit 2 (month 6)	1 (reference)	0.38
	Visit 3 (month 12)	0.79 (0.48 to 1.32)	
Baseline CD4 count	Per 100-cell/μL increase	0.94 (0.79 to 1.11)	0.45
MDD (lagged)	No	1 (reference)	0.001
	Yes	4.75 (1.87 to 12.04)	

TABLE 5. Results of Fitting Models to Outcomes Associated With MDD: Discrete Time Survival Model for Time to Visit to Health Facility

Factor	Level	Adjusted Odds Ratio (95% CI)	*P*
Study site	Entebbe	1 (reference)	<0.001
	Masaka	3.23 (2.33 to 4.49)	
Sex	Male	0 (reference)	0.23
	Female	1.26 (0.86 to 1.85)	
Age	Per 10-year increase	1.02 (0.86 to 1.20)	0.82
Visit	Visit 2 (month 6)	1 (reference)	0.015
	Visit 3 (month 12)	0.68 (0.49 to 0.93)	
Baseline CD4 count	Per 100-cell/μL increase	0.97 (0.91 to 1.02)	0.23
MDD (lagged)	No	1 (reference)	0.024
	Yes	1.71 (1.07 to 2.73)	

in risky sexual behavior at month 12. The results of fitting a discrete time survival model are summarized in Table 6. Adjusting for study site, sex, age, and baseline CD4 count, the odds of having engaged in risky sexual behavior were 2.11 times as high for participants with MDD (at the previous visit) compared with those without MDD (aOR = 2.11; 95% CI: 1.27 to 3.49; $P = 0.004$).

DISCUSSION

This, to our knowledge, is only the third article 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] Although each of the 2 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 4 HIV-related outcome domains of HIV disease progression, adherence to HIV medications, health-seeking behavior and risky sexual behavior.

TABLE 6. Results of Fitting Models to Outcomes Associated With MDD: Discrete Time Survival Model for Time to First Risky Sexual Behavior

Factor	Level	Adjusted Odds Ratio (95% CI)	*P*
Study site	Entebbe	1 (reference)	0.25
	Masaka	0.81 (0.56 to 1.16)	
Sex	Male	0 (reference)	0.003
	Female	0.55 (0.37 to 0.81)	
Age	Per 10-year increase	0.71 (0.57 to 0.88)	0.002
Visit	Visit 2 (month 6)	1 (reference)	0.64
	Visit 3 (month 12)	1.09 (0.76 to 1.55)	
Baseline CD4 count	Per 100-cell/μL increase	0.98 (0.92 to 1.05)	0.61
MDD (lagged)	No	1 (reference)	0.004
	Yes	2.11 (1.27 to 3.49)	

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 2 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 3 days. Although we feel this was a fairly robust finding, it is important to note that there were smaller numbers on ART compared with the cohort as a whole. In line with these findings, 2 previous systematic reviews have reported that depression negatively impacted ART adherence.[6,25] On health-seeking behavior, our findings were that having a previous episode of MDD was associated with a nearly two-fold increased risk of visiting a health facility. Although previous studies have reported MDD as a predictor of poor access to general HIV care services,[8] a multisite European study reported increased utilization of psychiatric services by individuals with MDD in the community.[26] The increased utilization of HIV care services that were associated with 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 PLWH. 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 behavior. Both Seth et al[9] among female African American adolescents in the United States of America and Nduna et al[12] among young adults in South Africa have reported MDD as a significant predictor of risky sexual behavior.

In conclusion, this study has demonstrated that MDD significantly impacted the HIV-related outcome domains of adherence to HIV medications, health-seeking behavior, and risky sexual behavior 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 behavioral outcomes. In addition, these results support an observation made by Collins et al[28] who in

a systematic review on the relevance of mental health to HIV/AIDS care and treatment programs in developing countries noted that behavioral factors including mental health disorders are likely to be a major determinant in ART roll. 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 behavior, and risky sexual behavior. There is however a need for more studies to further validate these findings in this sociocultural context.

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