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Kinyanda, E.; Weiss, H.A.; Levin, J.; Nakasujja, N.; Birabwa, H.; Nakku, J.; Mpango, R.; Grosskurth, H.; Seedat, S.; Araya, R.; Patel, V. (2016) [Accepted Manuscript] Incidence and Persistence of Major Depressive Disorder Among People Living with HIV in Uganda. *AIDS and behavior*. ISSN 1090-7165 DOI: <https://doi.org/10.1007/s10461-016-1575-7>

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Incidence and persistence of depression in HIV in Uganda

Incidence and persistence of major depressive disorder among people living with HIV in Uganda

Eugene Kinyanda^{1,2,3}, Helen A. Weiss³, Jonathan Levin⁴, Noeline Nakasujja², Harriet Birabwa⁵, Juliet Nakku⁵, Richard Mpango¹, Heiner Grosskurth³, Soraya Seedat⁶, Ricardo Araya³, Vikram Patel^{3,7}

Institutional Affiliation

¹Mental Health Project, MRC/UVRI Uganda Research Unit on AIDS/ MRC-DFID African Leadership Award, Entebbe, Uganda

²Department of Psychiatry, Makerere College of Health Sciences, Kampala, Uganda

³London School of Hygiene and Tropical Medicine, London, United Kingdom

⁴School of Public Health, University of the Witwatersrand, Johannesburg, South Africa.

⁵Butabika National Psychiatric Referral Hospital, Kampala, Uganda

⁶Department of Psychiatry, Stellenbosch University, Cape Town, South Africa

⁷Senior Wellcome Trust Fellowship, London, United Kingdom

Correspondent author

Eugene Kinyanda, Mental Health Project, MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda. P.O. Box 49 Entebbe, Uganda. Telephone: +256417704159; Email: Eugene.Kinyanda@mrcuganda.org .

Abstract

Data on the course of major depressive disorder (MDD) among people living with HIV (PLWH) are needed to inform refinement of screening and interventions for MDD. This paper describes the incidence and persistence rate of MDD in PLWH in Uganda. 1099 ART-naïve PLWH attending HIV clinics in Uganda were followed up for 12 months. MDD was assessed using the DSM IV based Mini-International Neuropsychiatric Interview with a prevalence for MDD at baseline of 14.0% (95% CI 11.7% -16.3%) reported. Multivariable logistic regression was used to determine predictors of incident and persistent MDD. Cumulative incidence of MDD was 6.1 per 100 person-years (95% CI 4.6-7.8) with significant independent predictors of study site, marital status, higher baseline depression score and increased stress. Persistence of MDD was 24.6% (95% CI 17.9%-32.5%) with independent significant predictors of study site, religion, higher baseline depression score, and increased weight. Risks of incident and persistent MDD observed in this study were high. Potentially modifiable factors of elevated baseline depressive scores and stress (only for incident MDD) were important predictors of incident and persistent MDD.

Key Words: HIV/AIDS, Major depressive disorder, incidence, persistence, predictors

Introduction

Major depressive disorder (MDD) is the most common neuropsychiatric complication among people living with HIV (PLWH) with prevalence ranging from 8% to 60% [1-7]. Negative impacts of MDD among PLWH include poorer quality of life, faster HIV disease progression, higher mortality, poor adherence to medication regimens, increased risky sexual behaviour, and perpetration of intimate partner violence [2,6-9]. Most studies of MDD among PLWH have been cross-sectional, and provided limited evidence on the course and aetiology of MDD due to the episodic nature of MDD [4,10] and the bi-directional relationship between MDD and HIV/AIDS [6]. Elucidating the course of MDD in HIV/AIDS and its predictors is important for refining screening procedures for MDD in HIV/AIDS and for the design and evaluation (including clinical trials) of intervention against MDD in HIV/AIDS.

Globally, a number of longitudinal studies on MDD among PLWH have been undertaken in both high-income countries [5,11-15] and in low and –middle income countries [4, 7, 9, 16-18]. However to date, only two such studies have been undertaken in sub-Saharan Africa [4,7]. Previous studies that have looked at the incidence of MDD in HIV/AIDS have reported rates of between 1.89 to 2.2 to per 100 person-years [17-18]. Most of the prospective studies (with none from a developing country context) that have included a non-HIV positive control group have reported no difference or only a slightly increased incidence of MDD associated with HIV [16-18]. From high income settings, predictors of incident MDD in PLWH included advanced HIV clinical stage, more frequent clinic visits, multiple psychiatric comorbidity, past history of MDD and social conflict, [3,12,13]. From developing country settings, predictors of incident MDD in PLWH included advanced HIV clinical stage, more frequent clinic visits, disability in work/social/family functioning, greater number of negative life events, decline in CD4 counts, HIV diagnosis made less than one year ago, being in HIV care for less than one year, having comorbid anxiety and female gender [4,16-18].

Similarly, there have been few studies on persistence of MDD among PLWH. In one of the pioneering studies in this area by Lyketsos and colleagues (1996) who followed up HIV positive

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patients not on antiretroviral therapy (ART) over a 10 year period reported a dramatic sustained rise in depressive symptoms beginning 18 months before the development of AIDS and peaking at diagnosis of clinical AIDS [11]. In a more recent South African study where 29 participants with HIV and MDD were followed up over 6-months, the risk of persistence for MDD was 44.8% [4]. Predictors of persistence of MDD in HIV/AIDS include elevated depressive symptoms in early stage disease, self-report of AIDS-related symptoms (fatigue and rash), concurrent unemployment, cigarette smoking, limited social supports and high baseline HIV symptom count [11,14].

This paper will describe the epidemiology of incidence and persistence of MDD among PLWH followed for 12 months in Uganda.

Methods

Study design and Site

This is a prospective cohort study where assessments were undertaken at baseline, 6-months and 12-months. This study was undertaken at two specialised HIV clinics run by the AIDS Support Organisation (TASO) at Entebbe (semi-urban) and Masaka (predominantly rural) [19]. The MRC/UVRI Uganda Research Unit (the host research institution) has an established research collaboration with these two study clinics. The TASO Entebbe clinic has approximately 7,000 active clients of whom about 3,000 are ART-naïve while the Masaka TASO clinic has approximately 6,000 clients of whom about 2,500 are ART-naïve.

Sampling Procedure

This study aimed to enrol 1100 ART naïve HIV positive adults from the TASO HIV clinics in Masaka and Entebbe (rural and semi-urban). We estimated that the sample size of 1100 respondents would allow us to estimate the actual incidence of MDD to a precision of about ± 1.4 per 100 PYO based on the following assumptions: the incident MDD cases will follow a Poisson distribution, baseline prevalence of MDD will be 11%; and incident rate of MDD will be 5 cases per 100 PYO. To obtain this sample, a sub-register of all active clients who were not on ART was created. From this register a

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random sample of 550 ART naïve patients was recruited from each clinic using a table of random numbers.

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 into which the research protocols were translated (the majority of respondents were not conversant with English the language in which the standardised assessment tools were developed). Exclusion criteria were being too sick or unable to understand the study instruments, and having defaulted on the most recent previous scheduled clinic visit. Eligible participants were asked for 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 tools most of which have previously been used among PLWH in the Ugandan setting by this study group [1]. The psychosocial assessment tools being employed for the first time in the Ugandan HIV setting were taken through a process of locally adaptation. This involved a process of forward and back translation by two teams of mental health professionals conversant with both English and the local language of translation (Luganda) working independent of each other. At a consensus meeting where both these teams were represented the final back translated English version was then compared to the initial English version. On those items where there was wide variation in the two versions, a consensus position was arrived at through discussion. The internal consistency of each of all the tools being used for the first time was determined by assessing their Cronbach's alpha and only those tools which had Cronbach's alpha of at least 0.7 were included in subsequent analysis for this study.

The data collection tools for this study were compiled together into the following groups: socio-demographic factors (Group 1), HIV associated clinical factors (Group 2A), vulnerability/protective factors (Group 2B), stressors (Group 2C) and the outcome measures of MDD as specified by the

conceptual framework for this study which is based on the stress-vulnerability model for depression (Figure 1) [20].

Insert Figure 1

A diagnoses of MDD was made using the DSM IV based Mini-International Neuropsychiatric Interview [31] while severity of depressive symptoms was assessed using the Centre for Epidemiological Studies-Depression questionnaire (CES-D) [32], the rest of the data collection tools are listed in Table I below.

Insert Table I

Statistical analysis

There were two dependent variables: i) incident major depressive disorder(MDD) assessed at 6-months and 12- months amongst those without MDD at baseline; and ii) persistent MDD over the 6-12 month follow-up among those with MDD at baseline (i.e. MDD detected at either 6 or 12 month follow-up). Logistic regression was used to estimate odds ratios and 95% CIs. A conceptual framework (see Figure 1) based on the stress-vulnerability models of depression [20] was developed *a priori* to guide the multivariable analysis [33]. Firstly, socio-demographic factors were included if there was at least weak evidence of a univariable association ($p < 0.15$). Factors were retained if they remained with $P < 0.15$ after adjustment for other socio-demographic factors. The liberal P-value cut-off was used in order to ensure that all variables that could have a possible confounding effect on the ultimate risk factors were included [34].

According to the conceptual framework, the socio-demographic variables (Group 1 variables) may act on MDD through three groups of proximal factors, a set of HIV associated clinical variables (Group 2A), a set of vulnerability/protective variables (Group 2B), and a set of stressor variables (Group 2C). In turn, the HIV associated clinical variables may act through Groups 2B and 2C as well

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as independently on MDD. Thus three second stage models were fitted, involving the selection of Group 1, and Group 2A, 2B or 2C variables respectively. The HIV associated clinical factors (Group 2A), vulnerability/protective factors (Group 2B), and stressor factors (Group 2C) associated with the outcome ($P < 0.15$) after adjusting for the Group 1 variables and baseline CES-D score were selected into an initial multivariable model. The final multivariable model included variables that were independently associated with the outcome ($P < 0.10$), using a backward elimination method. Part of the effect of the socio-demographic variables will be mediated through the vulnerability/protective variables, HIV associated clinical variables or through the stress variables, so the selected socio-demographic variables were not removed from the final model to capture both their direct and indirect effects [33]. For all continuous explanatory variables, we explored fractional polynomials of degrees 1 and 2 to investigate for potential nonlinearity [34].

Ethical Considerations

The study obtained ethical approval from the Uganda Virus Research Institute's Science and Ethics Committee, the London School of Hygiene and Tropical Medicine Ethical Committee and the Uganda National Council of Science and Technology. Study participants were invited to consent after being provided with adequate information about the study. Respondents found to have significant psychiatric problems were referred to the psychiatric departments at Entebbe district hospital (at the semi-urban site) and Masaka regional referral hospital (rural site) for further assessment and management.

Results

Of the 1099 participants assessed at baseline, 68 (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, gender, marital status and baseline MDD were associated with loss to follow-up.

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Amongst the 944 participants without MDD at baseline, 920 had follow-up data, and there were 56 incident cases over the 12 month follow-up period (6.1%; Table II). Amongst the 155 participants with MDD at baseline, 146 had follow-up data, including 36 persistent cases (24.7%), including 11 recurrent cases who were positive-negative-positive (Table II).

Insert Table II

Characteristics of study population

The majority (n=847, 77.1%) of the study respondents were female. The mean age was 35.1 years (standard deviation (SD)=9.3), and the majority were in early HIV stage disease (48.5% Stage 1; 45.5% Stage 2; 6.0% Stage 3) with the majority having CD4 counts above 350 cells/ul (< 201 cells/ul =9.4%; 201-350 cells/ul =15.3%; 351-500 cells/ul =30.5%;and >500=44.9%).

Incidence of MDD and risk of persistence of MDD

The cumulative incidence of MDD over 12 months in this study was 6.1per 100 person- years (95%CI 4.6-7.8). The risk of persistent of MDD over 12 months was 24.6% (95%CI 17.9%-32.5%).

Univariate predictors of incident MDD

Insert Table III

Table III shows factors associated with incident MDD. Among the socio-demographic factors, the only factor associated with incident MDD was study site (OR for Masaka vs Entebbe=4.35, 95%CI 2.27-8.36). After adjusting for study site, the following factors were associated with incident MDD: higher disability scores (OR=1.39, 95%CI 1.08-1.80); higher negative life events scores (OR=1.65,

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95% CI 1.25-2.17); and higher stress scores (OR=1.64, 95% CI 1.26-2.14); approaching significance were lower social support scores (OR=0.79, 95% CI 0.61-1.02) and baseline depressive symptom scores (OR=1.11, 95% CI 0.98-1.27).

Univariate predictors of persistent MDD

Insert Table IV

Table IV shows univariate predictor factors that were associated with persistent MDD. Among the sociodemographic factors, study site (Masaka-rural site) and religion were marginally associated with persistent MDD. Baseline depressive symptom scores were associated with persistent MDD after adjusting for study site and religion. After adjusting for study site, religion and baseline depressive symptom score (CES-D), the following variables were marginally associated with persistent MDD: lower CD count, a heavier weight, family history of psychiatric disorder (OR=2.25, 95% CI 0.98-5.12); higher negative life events score (OR=1.37, 95% CI 0.92-2.04) and higher stress scores (OR=1.34, 95% CI: 0.90-1.98).

Multivariate predictors of both incident MDD and persistent MDD

Insert Table V

Table V shows the independent factors associated with incident MDD and persistent MDD respectively. Living in the rural site (Masaka) was independently associated with both incident and persistent MDD, as was a higher baseline CES-D score. An increased stress score was associated with incident MDD (OR=1.56, 95% CI 1.18-2.05) and a heavier weight was associated with persistent MDD (OR=1.47, 95% CI 0.93-2.33).

Discussion

This is one of few papers that have investigated the incidence and persistence of major depressive disorder (MDD) and their predictors in HIV/AIDS in the sub-Saharan African setting. The loss to

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follow-up in this study was 6.2% (equivalent to 6.2 per 100 person-years) a figure much better than that reported by Olley and colleagues (2006) [4] in Cape Town, South Africa (56%) but lower than that reported by Elenka and colleagues (2013) [17] in Guadeloupe in central America (1.6 to 2.7 per 100 person-years). In this study the factors of study site, gender, marital status and baseline MDD were not associated with loss to follow-up. In Guadeloupe in central America, Elenka and colleagues (2013) [17] have suggested that addiction may have been a factor in loss to follow-up in their study, a factor that was not investigated in this study.

The incidence of MDD in HIV/AIDS in this study was 6.1 per 100 person-years) a figure higher than that reported in Guadeloupe in Central America (2.2 per 100 person years) [17] and French Guyana in South America (1.89 per 100 person years) [18], these two countries having generalised HIV epidemics similar to the HIV epidemic in sub-Saharan Africa. Differences in the incidence of MDD between this study and those two previous studies could be due to a number of factors including: differences in the assessment of MDD (in this study we used a DSM IV based structured interview-the M.I.N.I. [31] while in the two previous studies they used non-structured clinical interviews); differences in the risk for MDD associated with the parent HIV risk group (thought to be minimal as the HIV epidemic in all three studies was generalised); differences in the ecological risk factors for MDD and differences in the HIV clinical stage profiles of the three studies.

Predictors of incident MDD observed in this study included: study site (higher in the rural than urban site), greater disability, higher negative life events, higher stress and approaching significance were lower social support and baseline depressive scores. The independent predictors of incident MDD in this study were study site, elevated baseline depressive symptom scores and higher stress. Just as in this study, Olley and colleagues (2006) [4] in South Africa reported that disability in work, social and family functioning and a greater number of negative life events were predictors of incident MDD. Lyketos and colleagues (1996) [11] in the USA reported that elevated depressive symptom scores

were a predictor of higher rates of depression as AIDS developed. More recently, Atkinson and colleagues (2008) [5] reported that a past history of MDD was associated with a four-fold increased risk for developing incident MDD. Similar to this study, Lackner and colleagues (1993) [35] in a follow up study of male homosexuals at risk of HIV observed that social support only marginally accounted for future MDD episodes. A previous cross sectional study by this research group in semi-urban Entebbe (one of the study locations for this study) reported that increasing stress scores among HIV/AIDS patients was independently associated with prevalent MDD [1].

The association between study site and incident MDD observed in this study could not readily be explained. A possible explanation of this finding could be that study site represents ecological risk factors for MDD with this risk being greater in the rural area than in the urban area. Kinyanda and colleagues (2011) [36] in a community study that investigated district level indices to explain variation of district rates of MDD reported that only district literacy rates showed a reciprocal relationship with district rates of MDD. Comparing the two study sites on a few of the socio-economic indices collected in this study reveals the following pattern: on highest educational attainment, while 82% of study participants from Masaka (rural site) had seven years or less of formal education, the figure for Entebbe (semi-urban site) was 63% (a difference that was statistically significant); on socio-economic index (SEI), while the mean SEI of study participants from Masaka (rural site) was 13.9(SD=2.9) that for Entebbe (semi-urban site) was higher at 16.4 (a difference that was statistically significant). These results indicate that there are important socio-economic differences between the rural and urban study sites which may underlie the difference in incidence of MDD.

The risk of persistent of MDD over 12 months in this study was 24.6%. Olley and colleagues (2006) [4] in South Africa in one of the few studies in this area reported a 6-months rate of persistence of MDD in HIV/AIDS of 44.8%. The South African findings may have been confounded by the very high rate of loss to follow-up of 56%. On the flip side, 75.4% of the MDD cases in this study

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resolved by 12 months, the majority in less than 6 months (67%). Similar results to those observed in this study have been reported in a general population cohort study in the Netherlands (the NEMESIS Study) where Spijker and colleagues (2002) reported that 76% of their study participants recovered from MDD by 12 months with the majority (63%) of these recovering by 6 months [10]. Whiteford and colleagues (2013) in a systematic review on spontaneous remission of untreated MDD reported that 53% of untreated cases of MDD remitted by 12 months while 32% remitted by 6 months [37].

Apart from the natural life cycle of MDD, other possible reasons for the high remission rates of MDD observed in this study include that all participants diagnosed with MDD were offered health education about MDD (psychoeducation is known to be effective against MDD [38]) and then referred to the nearest health facility that offered mental health care. Secondly, 43% of the study participants initiated antiretroviral therapy (ART) during the course of this study. Initiation of ART has previously been reported by Wagner and colleagues (2012) in the HIV care situation of Uganda to be associated with a significant reduction in depressive symptoms mainly mediated through improvement in physical health functioning [39].

In this study baseline depressive symptoms and marginally, study site (rural-urban difference), religion, a heavier weight, a family history of psychiatric disorder, higher negative life events and higher stress were associated with persistent MDD. At multivariate analysis study site, elevated baseline depressive scores and a heavier weight were independently associated with persistent MDD.

Of the observed predictor factors for persistence of MDD in HIV/AIDS in this study, only elevated depressive symptoms in early stage disease has previously been reported to be associated with persistent MDD in HIV/AIDS [11]. In this study, heavier weight was a predictor of persistence of MDD, an association that has not been previously reported. Unlike the results from this study, the few adult prospective studies undertaken among non HIV populations reveal that MDD is more likely to elevate the risk of subsequent obesity than the converse [40-42]. From non HIV studies, stressful life

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events have been reported to be a predictor of persistent MDD [43-44]. Just like in this study where a family history of psychiatric disorder was associated with persistent MDD, Lieb and colleagues (2002) in a German community study of adolescents and young adults reported that parental depression was associated with a more malignant course of depressive disorders in offspring [45]. The association between study site and persistence of MDD in this study probably points to the importance of ecological level factors in the persistence of MDD in HIV/AIDS in the African socio-cultural context.

In conclusion, on the incidence of MDD, the rate obtained in this study was higher than that reported in two previous studies undertaken in Guadeloupe (in Central America) and French Guyana (in South America), countries with generalised HIV epidemics like that in Uganda, this probably points to differences in ecological risk factors for MDD. Secondly, the potentially modifiable factors of elevated baseline depressive scores and increased stress scores were independent predictors of incident MDD in this study. The later findings have at least two implications for depression management, firstly, that elevated depressive scores (even those that are below the threshold for MDD diagnoses) are a risk factor for future MDD episodes and should therefore be screened for and managed. Secondly, that stress (number and severity of negative life events in the previous 6 months) is risk factor for future MDD episodes and hence should be included in the risk assessment for MDD and where elevated managed.

In this study we reported rates of persistence of MDD that were similar to those reported in a non-HIV community sample in the Netherlands. The fact that about a quarter of the cases of MDD in this study were persistent at 6 months and up to 12 months and given the potentially negative clinical and psychosocial consequences of MDD reinforces the need to treat MDD in HIV/AIDS even in this African socio-cultural context. On the flip side however, given that three quarters of the cases of MDD remitted without instituting formal MDD treatment and given the severe challenges facing health systems in low and-middle income countries such as Uganda [46-47] calls for caution in the

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recommendations we make for the management of MDD in such settings. In such settings there is need to institute stepped care collaborative management approach for MDD where low intensity therapies such as psychoeducation [48] and the Health Activity Programme [49] with demonstrated efficacy against MDD even when administered by lower level cadre such as general nurses and lay health workers can be offered to those with mild to moderate MDD and antidepressant medication and referral to mental health specialists offered to those with severe MDD. However, there is need for studies to develop and evaluate such stepped care collaborative models in the context of the health systems challenges facing HIV care services in sub-Saharan African settings such as those in Uganda. Lastly, there is need for studies to specifically delineate the factors underlying ecological risk for MDD in HIV/AIDS, and more broadly, to better understand ecological correlates of mental illness in the African situation.

As a limitations of this study, exclusion from enrolment of those with recent defaulted appointments may have introduced selection bias because MDD is a known risk factor for non-adherence with medical treatment [50]. Secondly, in designing this study, we assumed that the majority of MDD episodes run a cycle of 6 months based on previous work undertaken in the west among HIV negative general population samples [10]. Indeed in this study, the majority of MDD episodes (67%) went into remission by 6 months although a small number (8.4%) went into remission between 6 and 12 months.

Acknowledgement

This study was supported by a Senior Fellowship to Eugene Kinyanda from the European & Developing Countries Clinical Trials Partnership (EDCTP) Project No. TA.2010.40200.011. We acknowledge the work and support provided by staff of the MRC/UVRI Mental Health Project. We would also like to acknowledge the support and corporation by the management and clients of The AIDS Support Organisation (TASO) Service Centres of Entebbe and Masaka.

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