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Major depressive disorder and suicidality in early HIV infection and its association with risk factors and negative outcomes as seen in semi-urban and rural Uganda

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ABSTRACT

Introduction: There is a paucity of research into the psychiatric problems associated with early stage HIV clinical disease in sub-Saharan Africa.

Methods: A cross sectional study was undertaken among 899 adult ART naïve persons in early stage HIV clinical disease (participants with $CD4 \geq 250$ and who were at WHO clinical Stage I or II) attending a semi-urban and a rural clinic in Uganda.

Results: The prevalence of major depressive disorder in this study was 14.0% [95% CI 11.7% - 16.3%] while that of 'moderate to high risk for suicidality' was 2.8% [95% CI 1.7% ; 3.9%]. Multivariable analyses found that factors in the socio-demographic, vulnerability/protective and stress (only for major depressive disorder) domains were significantly associated with both major depressive disorder and 'moderate to high risk for suicidality'. Major depressive disorder but not 'moderate to high risk for suicidality' was significantly associated with impaired psychosocial functioning, greater utilisation of health services and non-adherence to septrin/dasone. Neither major depressive disorder nor 'moderate to high risk for suicidality' was associated with CD4 counts, risky sexual behaviour nor with non-utilisation of condoms.

Limitations: The bidirectional nature of some of the relationships between the investigated psychiatric problems, risk factors and outcomes in this cross sectional study makes it difficult to elucidate the actual direction of causality.

Conclusion: Early stage HIV clinical disease is associated with considerable major depressive disorder and 'moderate to high risk for suicidality'. Therefore there is a need to integrate mental health into HIV interventions that target early stage HIV disease.

Key Words: HIV/AIDS, Major depressive disorder, suicidality, risk factors, negative outcomes

BACKGROUND

Most of the research into psychiatric problems in HIV/AIDS in Africa has been undertaken during late stage HIV clinical disease with a dearth of research during the earlier stages of HIV infection. This is despite the fact that the pattern of psychiatric problems and its associated risk factors varies along the HIV disease course (Musisi and Kinyanda, 2009; Fernandez and Ruiz, 2006). Additionally, from studies undertaken in the West among newly diagnosed persons living with HIV (PLWH), psychiatric problems such as major depressive disorder have been reported to be highly prevalent and to be associated with the negative clinical and behavioural outcomes of poor linkage to HIV care, more likely to report barriers to appointment adherence and high risk sexual behaviour (Bhatia et al, 2012; Metsch et al, 2008). However, two recent policy changes in HIV prevention and treatment including in sub-Saharan Africa are going to increasingly bring PLWH into contact with HIV care services while they are still in early stage disease. These policy changes include firstly, that many countries in sub-Saharan Africa are in addition to providing Voluntary HIV Testing (VCT) also embracing Routine HIV Testing (RHT) in all clinical encounters and in home based settings (Ministry of Health, Uganda, 2010; National Department of Health, Republic of South Africa, 2009). Secondly, the WHO in 2015 recommended that all people living with HIV should be offered antiretroviral therapy irrespective of their CD4 counts (WHO, 2015). Therefore in the sub-Saharan African context, there is a need to better understand the pattern and magnitude of the psychiatric problems in early stage HIV disease, their risk factors and their impact on clinical and behavioural outcomes. In response to this need, the Mental Health Project at the MRC/UVRI Uganda Research Unit on AIDS undertook a study to investigate psychiatric problems among HIV positive patients in early stage HIV clinical disease. We looked at the burden of two of the commonest psychiatric problems (major depressive disorder and suicidality) reported in this setting (Kinyanda et al, 2011a; Kinyanda et al, 2012a) and assessed their association with a broad range of explanatory risk factors and potential negative health consequences. The results of this study are presented in this paper.

METHODS

Study design and Site

This was a cross sectional study undertaken at two specialised HIV clinics run by the AIDS Support Organisation (TASO) at Entebbe (semi-urban) and Masaka (predominantly rural) (TASO, 2014). 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 7,000 active clients of whom about 3,000 are ART naïve while the TASO Masaka clinic has 6,000 active clients of whom about 2,500 are not on ART. The study was conceived as a multisite study in which the analysis would combine the data over the two sites.

Sampling Procedure

A sample size of 1100 respondents was estimated to be sufficient to determine the prevalence of the investigated psychiatric problems (major depressive disorder (MDD) and ‘moderate to high risk for suicidality’ (MHS) with a precision of at least 2%, assuming that the true prevalence was in the order of 11%. To arrive at this estimated prevalence, we used rates of psychiatric problems from a previous study undertaken by this research group in the semi-urban district of Entebbe (one of the study sites of this project) where a rate of 8.3% for MDD (Kinyanda et al, 2011a) and 7.8% for MHS (Kinyanda et al, 2012a) were obtained. These rates were then adjusted to 11% for each psychiatric problem to take care of the anticipated higher prevalence at the rural site. To obtain this sample, a sub-register of all active clients who were not on ART was created at each of the study sites. From each sub-register, a random sample of 550 ART naïve patients was selected using a table of random numbers to give a combined study sample of 1100. We did not collect information to estimate participation rate.

Inclusion Criteria: i) A person who was living with HIV (PLWH) who was ART naïve and registered with the outpatient clinic at either TASO Entebbe and TASO Masaka clinics; ii) was an adult at the time of enrolment (at least 18 years old); iii) was conversant with Luganda, the language into which the research protocols were translated; iv) gave informed consent after adequate explanation of the study objectives, procedures and expected benefits.

Exclusion Criteria: i) was too sick (those patients who come to the HIV clinics with severe physical health problems and are unwell and need emergency assessment and hospitalisation)] and ii) unable to understand the study instruments.

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 (Kinyanda et al, 2011a, 2012a). The data collection tool was administered by trained psychiatric nurses who were supervised by a psychiatrist (E.K.). The psychosocial assessment tools being employed for the first time in the Ugandan HIV setting were taken through a process of local 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 0.4 were included in subsequent analysis for this study.

insert Figure 1

The data collection tools for this study were compiled together into the following groups (see conceptual framework in figure 1): socio-demographic factors (Group 1); vulnerability/protective factors (Group 2A); stressors (Group 2B); psychiatric outcomes (Group C); and negative clinical and behavioural outcomes (Group 3). The composition of these groupings was underpinned by the stress-vulnerability hypotheses of depression and suicidality (Monroe and Simons, 1991; Mann et al, 1999; Wasserman, 2001) which state that depression and suicidality will develop only when stress factors act on an underlying vulnerability (see figure 1). Psychiatric problems were assessed using the M.I.N.I. neuropsychiatric interview (MINI Plus) which is a modular DSM IV based structured

interview (Sheehan, 2000). The two psychiatric problems that were assessed for this study were: current major depressive disorder (MDD) as defined by DSM IV in the MINI Plus module; and ‘moderate to high risk for suicidality’ (MHS) as defined in the suicidality module of the MINI Plus to be a score of nine and above on the suicidality items of the MINI Plus module on suicidality, we broadened this definition to also include those who had attempted suicide in the last month despite not attaining the score threshold of nine on the suicidality module of the MINI Plus’. The other data collection tools are described in Appendix 1.

Statistical analysis

In this study there were two sets of dependent variables, namely the psychiatric problems variables - major depressive disorder (MDD) and moderate to high risk for suicidality (MHS) and the clinical and behavioural outcomes variables (see Appendix 1). For the psychiatric problems outcomes, the prevalence of MDD and MHS were estimated together with exact binomial 95% confidence limits. To undertake the analysis for this study, the approach recommended by Victoria et al. (1997) for multivariable analysis was used. Firstly, the association of socio-demographic factors was investigated through the use of a backward elimination logistic regression model, choosing the candidate variables based on prior knowledge and plausibility, and using a liberal P-value (15%) for removal, in order to ensure that all variables that could have a possible confounding effect on the ultimate risk factors were included, as recommended by Royston et al. (1999).

According to the stress-vulnerability hypotheses for depression and suicidality (Monroe and Simons, 1991; Mann et al, 1999; Wasserman, 2001), the socio-demographic variables (Group 1 variables) act independently on two groups of proximal factors, namely a set of vulnerability /protective variables (Group 2A variables) and a set of stressor variables (Group 2B variables). Thus two second stage models were fitted, the first involving the selected Group 1 and Group 2A variables, while the second involved the selected Group 1 and Group 2B variables. In each case variables were removed from the logistic regression model using a backward elimination algorithm with a stricter 10% nominal P-value for removal, always keeping the selected Group 1 variables in the model. The vulnerability/protective

factors (Group 2A) and stressor factors (Group 2B) selected in this way were then kept in the final logistic regression model, together with all selected Group 1 variables. As pointed out by Victoria et al. (1997), part of the effect of the socio-demographic variables will be mediated through the vulnerability / protective variables or through the stress variables, so in the case of MDD, none of the selected socio-demographic variables were removed from the final model. In the case of MHS, variables that were no longer significant at the 10% level were removed and employment status was dichotomised as employed vs. unemployed, since only 25 participants had moderate to high suicidality and an informal rule of thumb suggests about 5 cases for each variable included in the final model. For all continuous explanatory variables the possibility that the underlying relationship between the outcome and the variable is not linear was investigated by fitting fractional polynomials of degree 1 to find the best form of the relationship between the outcome and the explanatory variable. This was done by choosing the power transformation x^p with the power p chosen from the candidates $\{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ where x denotes $\log(x)$. The non-linear function was preferred only if a test of $p=1$ against the best fitting model with $p \neq 1$ was statistically significant at the 5% level. The test was performed by comparing the difference in model deviances with a χ^2 distribution on 1 d.f. (Royston et al, 1999). For the descriptive tables only, the continuous explanatory variables were categorised in order to see any apparent trends in the outcome variables. Interactions between those exposures found to be significant predictors of MDD or MHS and study site were investigated in order to justify combining the data across the two study sites.

The negative behavioural outcome variables (Group 3) were regarded as either ordinal (days of normal activity disrupted in the last month, number of times a Health Unit was visited in the last month, number of days admitted to Hospital in the last month and the high risk sexual behaviour index) or binary (whether Septrin / Dapsone treatment had been missed in the previous three days, whether the participant had engaged in any high risk sexual behaviour and whether those participants who had engaged in high risk behaviour had done so without using a condom). In the case of the ordinal outcomes, ordinal logistic regression models were fitted to investigate whether the outcome was associated with MDD or MHS, while for the binary outcomes logistic regression models were fitted. In each case, on the basis of prior knowledge, it was decided to adjust for study site, age, sex,

educational level and most recent CD4 count (in the past 6 months). Fractional polynomials of degrees 1 and 2 were explored to investigate potential nonlinearity in the response to age and CD4 count (Royston et al., 1999).

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 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

Prevalence of major depressive disorder (MDD) and 'moderate to high risk for suicidality' (MHS)

Out of the 1100 study participants enrolled in this study, 201 (18.3%) were excluded from this analysis because they either had a CD4 count of less than 250 or were at WHO stage III or IV (were in late stage HIV disease). Out of 899 participants included in the analysis, 126 had major depressive disorder (MDD), a prevalence of 14.0% (95% CI 11.7% - 16.3%). The prevalence was higher in Masaka (rural site) than in Entebbe (urban site). In Masaka 92/473 had MDD, giving a prevalence of 19.5% (95% CI 15.9% - 23.0%), while in Entebbe 34/426 had MDD giving a prevalence of 8.0% (95% CI 5.4% - 10.6%).

Overall 25 participants had 'moderate to high risk for suicidality' (MHS), a prevalence of 2.8% (95% CI 1.7% - 3.9%). The prevalence of suicidality was slightly higher in Masaka (17/473) giving a prevalence of 3.6% [95% CI (2.1% - 5.7%)] than in Entebbe (8/424) giving a prevalence of 1.9% [95% CI (0.8% - 3.7%)]. Of the 25 participants who had MHS, 20 also had comorbid MDD, thus

106 (11.8%) had MDD only, 5 (0.6%) had MHS only and 20 (2.2%) a comorbidity of both MDD and MHS.

Factors associated with MDD and MHS

Insert Table 1

Tables 1 and 2 give the prevalence of MDD and MHS broken down by the levels of potential explanatory factors; for the purpose of these descriptive tables only, the continuous explanatory variables have been categorized.

Insert Table 2

Factors associated with MDD

From Table 1, at bivariate analysis, the following baseline factors were associated with MDD: study site (higher in the rural site compared to the urban site); sex (higher among females compared to males); and employment status (highest among the unemployed/ retired group compared to the other employment categories). From Table 2, at bivariate analysis, the following psychosocial factors were associated with MDD: increasing childhood trauma scores, increasing negative coping style scores, food insecurity, increasing negative life events scores, increasing stress scores, increasing HIV stigma scores, higher HIV dementia scores, decreasing resilience scores and decreasing social support scores.

Insert Table 3

Table 3 shows the results of fitting multiple logistic regression models guided by the stress-vulnerability hypothesis of depression (Monroe and Simons, 1991) to find factors associated with MDD. The group 1 variables chosen were study site, age and sex. The group 2A variables chosen were stigma score, childhood trauma score, negative coping score and resilience score; the use of fractional polynomials showed that the effect of resilience score was non-linear. The only group 2B variable chosen was the negative life experiences score. This process led to the final model shown in Table 3. The odds of MDD were more than three times higher in Masaka than in Entebbe and were

higher for females. The odds of MDD increased with increasing stigma score, increasing childhood trauma score, increasing negative coping score and increasing negative life experiences score. The odds of depression decreased with increasing resilience score, but the effect was nonlinear and became weaker with increasing resilience, with the effect being most marked at resilience scores below 50. Note that Victoria et al (1997) point out that group 1 variables should remain in the model even if the effect is no longer statistically significant (such as the effect of age here), as the effect of such variables is mediated through other variables. Interactions were investigated between the exposures included in the final model for MDD and study site. None of the interactions were found to be significant at the 5% level.

Factors associated with MHS

From Tables 1 and 2, at bivariate analysis, the following baseline factors were associated with MHS: employment status (highest among the unemployed/retired group compared to the other employment categories); and the psychosocial factors of increasing HIV stigma scores, increasing negative coping style scores, decreasing resilience scores and decreasing social support scores.

insert Table 4

Table 4 shows the results of fitting multiple logistic regression models guided by the conceptual framework, to find factors associated with MHS. The group 1 variables chosen were study site, SES index and employment status; due to the small number of cases there was a need to restrict the number of terms in the model, thus employment status was recoded as unemployed / retired vs. others. The group 2A variables chosen were current depression (on the modified depression scale), felt stigma score and resilience score; the use of fractional polynomials showed that the effect of resilience score was nonlinear. No group 2B variable was chosen. This process led to the final model shown in Table 4. The odds of MHS were lower in Masaka than in Entebbe. The odds of MHS decreased with increasing SES score. The odds of MHS increased with increasing felt stigma score and were over seven times as high for participants with current depression (on the modified scale). The odds of MHS decreased non-linearly with increasing resilience score, with the effect being

strongest for resilience scores of 40 or below. Interactions were investigated between the exposures included in the final model for suicidality and study site. None of the interactions were found to be significant at the 5% level.

Association of MDD and MHS with negative outcomes

Ordinal logistic regression models or logistic regression models were fitted as appropriate to find whether MDD or MHS were associated with negative functional or behavioural outcomes, adjusting *a priori* for study site, sex, age, CD4 cell count and educational level. Table 5 shows the association of MDD and MHS with the negative outcomes.

Insert Table 5

None of the negative outcomes was significantly associated with MHS in this study. Participants with MDD had more than double the odds of having a greater number of days disrupted compared to those without MDD. There was some evidence ($P=0.071$) that participants with MDD had higher odds than those without MDD of having a greater number of visits to a Health Unit. Participants with MDD had over three times the odds of being admitted to a health facility for a larger number of days than participants without MDD. Participants with MDD had a significantly higher odds than participants without MDD of having missed a dose of Septrin / Dapsone. The associations of MDD with the number of risky sexual behaviours, with having engaged in any risky sexual behaviour and with having engaged in risky sexual behaviour without using a condom were not statistically significant, although the associated odds ratios were suggestive of a possible association.

DISCUSSION

On the prevalence of the investigated psychiatric disorders, the burden of major depressive disorder (MDD) in this study was high at 14.0%, with the rate of MDD at the rural site of Masaka (19.4%) twice that seen at the semi-urban site of Entebbe (8.0%). The rate of MDD of 8.0% reported at the semi-urban site was very similar to the rate of 8.1% that was reported in a previous study in the same district that was carried out at two government run HIV clinics among a predominantly late stage HIV

clinical disease sample (Kinyanda et al, 2011a). These results suggest that rates of MDD in early stage HIV clinical disease may be similar to those in late stage HIV clinical disease.

In this study, the overall prevalence of those who had a ‘moderate to high risk for suicidality’ (MHS) was 2.8% with the rate of 3.6% observed in rural Masaka and a rate of 1.9% in semi-urban Entebbe. Two previous studies undertaken in predominantly late stage HIV clinical disease samples attending HIV care services at two semi-urban sites (Entebbe and Mbarara districts) in Uganda reported rates of MHS of 7.8% (Kinyanda et al, 2012a) and a rate of 8.8% for suicidal ideation and 3.1% for suicide attempt (Rukundo et al, 2016) which were much higher than those reported in this study. These results suggest that early stage HIV clinical disease may be associated with lower rates of MHS compared to late stage HIV clinical disease. Eighty percent of the respondents with MHS had comorbid MDD, a previous study undertaken by this research group among HIV positive patients reported a significant association between suicidality and the psychiatric diagnoses of post traumatic stress disorder, generalised anxiety disorder and major depressive disorder but not alcohol dependency disorder (Kinyanda et al, 2012a). Jia and colleagues (2012) examining the national registers in Denmark similarly observed that comorbidity between HIV/AIDS and psychiatric illness increased the risk of suicide.

The risk factors significantly associated with MDD from a multivariable analysis were in the three domains of the conceptual framework underlined by the stress-vulnerability model for depression (Monroe and Simon, 1991), namely: socio-demographics (study site); vulnerability/protective factors (childhood trauma, HIV felt stigma, negative coping scale and low resilience); and stress factors (negative life experiences score). None of the investigated clinical factors (family history of mental illness, CD4 counts and WHO clinical stage) nor neurocognitive impairment were significantly associated with MDD in a multivariable analysis. These findings are in agreement with previous research which has documented the following risk factors for MDD in HIV/AIDS, negative coping style, childhood trauma, low resilience, stress and stigma (Kinyanda et al, 2012a; Koopman et al, 2000; Simoni and Ng, 2000; Spies and Seedat, 2014; Judd et al, 2005; Vyavaharkar et al, 2010). The

variable 'study site' which was independently associated with MDD seems to represent ecological factors. Possible ecological level factors that would explain the higher rates of both MDD and MHS observed at the rural site compared to the semi-urban site include more difficult life conditions including a greater risk to economic shocks (such as crop failure) in rural areas compared to urban areas and poorer access to social amenities (such as health care, transport and schooling) in the rural areas compared to the urban areas. There is however a need for more studies to investigate the ecological level factors that are associated with psychiatric problems in HIV/AIDS in the sub-Saharan African setting.

The risk factors significantly associated with MHS at multivariate analysis were in only two of the domains of the conceptual framework that was underlined by the stress-vulnerability model of suicidality (Mann et al, 1999; Wasserman, 2001), namely, socio-demographic factors (indices of low social economic status- the SES score and unemployment) and vulnerability/protective factors (depression, HIV felt stigma and low resilience). These findings are in agreement with previous research which has documented the following risk factors for MHS in HIV/AIDS, low socio-economic status, unemployment, low resilience, stigma, and depression (Aschan et al, 2013; Qin et al, 2003; Roya et al, 2007; Schlebusch and Vawda, 2010; Kinyanda et al, 2012a). In this study none of the investigated stress factors nor clinical factors were significantly associated with MHS at multivariate analysis unlike in the previous study undertaken by this research group (Kinyanda et al, 2012a). In the MHS analysis, failure to attain statistical significance for some of the investigated factors could have been attributed to the low study power which was due to the small number of study participants (25/899) who met criteria for MHS in this study.

In this study MDD but not MHS was significantly associated with impaired psychosocial functioning, more utilisation of health services and non-adherence to Septrin / Dapsone. Neither MDD nor MHS was associated with high risk sexual behaviour in this study. Previous studies have reported the association between MDD and psychosocial impairment in HIV/AIDS (Kinyanda et al, 2011a),

increased utilisation of psychiatric services (McCracken et al, 2006), and non-adherence to HIV/AIDS treatment (Gonzalez et al, 2011).

In conclusion, the results from this study seem to suggest that early stage HIV clinical disease is associated with a rate of MDD similar to that reported in late stage HIV clinical disease but a rate of MHS that is lower than that reported in late stage HIV clinical disease. Secondly, MDD but not MHS was associated with risk factors in all the domains of the conceptual framework (that is underlined by the stress-vulnerability model) suggesting that MDD but not MHS in this study is better fitted to the hypothesized stress-vulnerability model. Lastly, MDD but not MHS was associated with negative clinical and behavioural outcomes in this study. The translated standardised clinical assessment tools used in this study although not taken through a formal validation process were associated with good indices of internal consistency suggesting that they were good measures of the stated constructs in this African socio-cultural context.

On study limitations, this having been a cross-sectional study, the actual direction of causality between the psychiatric problems and the investigated risk factors and negative outcomes could not be determined because some of these relationships are bi-directional, hence the need for longitudinal studies (Collins et al, 2006). This study did not include alcohol and substance abuse data which are potential risk factors of both MDD and suicidality. However, previous work undertaken by this research group in one of the study districts showed very low rates (0.7%) of alcohol abuse disorders among persons living with HIV hence the decision not to include these variables in this study (Kinyanda et al, 2011a).

Another limitation of this study is that the psychological assessment instruments being used for the first time were not taken through a formal validation process but were however taken through a process of forward and backward translation and were required to meet a minimum threshold on the reliability index before they could be employed in further analysis in this study. On limitations associated with the modelling strategy used in this study, in order to reduce the shortcomings of

automatic variable selection we followed a strategy in which the variables were added to the model in groups, starting with the group of variables deemed to be most distal to the outcome. We also restricted the pool of potential explanatory variables using prior knowledge and scientific plausibility.

On clinical relevance of this study, since this study has shown that the prevalence of MDD and MHS in early stage HIV clinical disease is considerable, there is need to integrate mental health care in all HIV care programmes targeting persons in early stage HIV clinical disease. Secondly, since the risk factors of MDD and MHS observed in this socio-cultural setting include social, psychological and socio-economic factors, there is need for a multifaceted approach to mental health prevention in HIV/AIDS in this socio-cultural context. Thirdly, since MDD in this study has been shown to negatively impact the HIV outcomes of psychosocial functioning, adherence and service utilisation, programmes targeting these HIV outcomes should include screening and management of MDD.

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