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Prevalence and Correlates of Major Depressive Disorder among Human Immunodeficiency Virus Infected Adults in Sub-Saharan Africa: A Systematic Review and Meta-analysis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AGH, AMY, LFO, AI and MIG designed the study. Authors AMY, AI, MIG, HM, ASS, MMY and MN managed literature searches. Authors AMY and AI independently assessed the studies and extracted the data and author AGH resolved the disagreements. Authors AMY, MBM, ZGH, SS and AGH performed the statistical analyses. Author AMY wrote the protocol, and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Although major depressive disorder (MDD) is the commonest psychiatric complication of HIV infection, its prevalence and correlates are not fully evaluated in Sub-Saharan Africa (SSA).

Methods: PsychInfo, Medline and Google scholar were among the data bases searched for relevant publications up to December 2013. Assessments of study quality, heterogeneity test (I^2 statistics) and sensitivity analysis were performed. We used random-effects model (REM) meta-analysis to derive pooled estimates of MDD in SSA. Statistically significant p-value in both Egger's and Begg's tests denote publication bias.

Results: The prevalence (95% confidence interval [CI]) of MDD among HIV infected subjects was 17.3% (11.65-22.97). Symptomatic patients with Acquired immune deficiency syndrome (AIDS) had significantly higher prevalence than asymptomatic patients (17.5% and 8.3% respectively, P = .036). Odds Ratio [OR] (95% CI) of correlates of MDD were: HIV infection = 3.1 (1.97-4.17), female gender = 1.71 (1.09-2.32), Tuberculosis (TB) = 2.34 (1.0-5.63), food insecurity = 2.89 (1.40-5.89), higher income = 0.68 (0.45-1.0) and high social support = 0.75 (0.60-0.90).

Conclusion: HIV infection is associated with development of MDD and AIDS patients are mostly afflicted. Preventing disease progression and improving the social welfare of patients are interventions needed to reduce the burden of MDD among HIV-infected subjects in SSA.

Keywords: HIV; Major depressive disorder; Sub-Saharan Africa; prevalence; correlates; systematic review; meta-analysis.

1. INTRODUCTION

Major depressive disorder (MDD) is the most common psychiatric complication associated with HIV infection [1,2] and a frequent adjustment reaction following diagnosis [3]. Diagnosis of HIV is often associated with catastrophic consequences including social stigma, marital separation, low self esteem, breakdown of family, unemployment and poor quality of life [4]. Subsequently the negative impact of depression on both the immune system and patient's behavior can determine the course and outcome of HIV infection [5-7].

The prevalence and correlates of MDD in Sub-Saharan Africa (SSA) are not fully evaluated. The reported prevalence of depression using screening instruments in SSA ranged from 2.7%–83.3% [7,8] while using standardized diagnostic tools the prevalence ranged from 2.5%–54.3% [9,10]. Sociodemographic and clinical factors could affect the prevalence of depression and they should be routinely assessed by clinicians and other healthcare providers to identify patients at risk of MDD who may require special attention and referral to a psychiatrist. A previous systematic review of studies conducted in SSA had evaluated depression in relation to alcohol use and adherence to antiretroviral therapy [11]. In that review only studies from 2006 were included because antiretroviral therapy was freely available in most countries in SSA around that time. Thus several high quality studies were excluded and inconsequence could not assess very important modifiers of MDD among HIV infected subjects. We conducted this systematic review and meta-analysis to provide pooled estimates of prevalence of MDD among HIV infected subjects and explore its clinical and sociodemographic correlates. Determining the prevalence and correlates of MDD among people living with HIV/AIDS (PLWHA) could have social and economic implications to HIV/AIDS treatment and control in SSA.

2. METHODS

2.1 Article Search and Inclusion Criteria

English language publications were searched in PsychInfo, Medline, Google scholar, African Journal Online (AJOL), Cochrane database, EMBASE and Web of science. Systematic reviews and relevant books and chapters were also searched. References of identified studies were also searched manually. Medical Sub-Heading (MeSH) terms used in search include; 'Africa', 'HIV', 'AIDS', ''adults', depression', 'major depressive disorder', 'mood disorders', 'neuropsychological disorders', 'neuropsychiatric disorders', 'mental disorders', 'psychological disorders', 'psychiatric disorders', 'psychosocial disorders', 'emotional disorders', 'behavioural disorders', 'neuro-psychological impairment',

'correlates', 'predictors', 'risk factors', 'determinants,' 'Sub-Saharan Africa' and 'studies'. These were applied in different combinations in search of relevant publications up to December 2013. Two reviewers assessed each study independently and where there is disagreement a third reviewer is consulted. The inclusion criteria were:

1) All participants should be ≥18 years of age;
2) Prospective or cross-sectional studies that used standardized diagnostic interview for assessment of depression among HIV-infected subjects in SSA;
3) Studies that provided current point prevalence and/or correlates of MDD.

Excluded were studies that did not provide correlates of MDD, current prevalence of depression or only provided life time prevalence, reported maternal or postpartum depression, reviews and dissertations.

2.2 Study Quality and Reporting Format

This meta-analysis was done and reported according to specific guidelines/checklist: "Meta-analysis of Observational Studies in Epidemiology" (MOOSE) [12] and "Preferred Reporting Items for Systematic Reviews and Meta-analysis" (PRISMA) statements [13]. The Downs and Black checklist was used to assess study quality [14].

2.3 Data Extraction

The following items were extracted and recorded into a standardized form: Authors, country, year of publication, setting, study design, sample size, structured diagnostic interview, diagnostic criteria, mean/median age, HIV status, symptom status, years of formal education, mean/median CD4 cell counts, viral load, overall proportion of participants with depression, proportion of participants with depression by gender, proportion of participants on antiretroviral therapy (ART), correlates of MDD, potential confounders and possible sources of bias were recorded.

2.4 Data Analysis

For the HIV- infected and HIV- negative subjects the prevalence of MDD, standard error and 95% confidence interval (CI) were calculated for each of the included studies. For studies that reported no cases of MDD in one of the comparison groups, continuity correction was done by adding 0.5 to the numerator and denominator of all the groups [15]. Odds ratio (OR) and respective 95% CI for MDD were extracted or calculated for comparison groups. The degree of statistical heterogeneity was assessed with *I*-squared (I^2) statistics (I^2 >50% indicates substantial heterogeneity). When between-study heterogeneity is not statistically significant we used a Fixed Effects Model (FEM) to derive pooled estimates whereas if between-study heterogeneity is statistically significant a Random Effects Model (REM) is applied. Egger's regression asymmetry test together with funnel plots generated from Begg's and Mazumdar's adjusted rank correlation tests were used to evaluate publication bias and small study effect [16,17]. Because these tests could be unpredictable, publication bias was assumed present only if detected in all the tests [18,19]. Sensitivity analysis was done to examine the influence of individual studies on the pooled estimates. Statistical analyses were carried out using Stata version 12.0 (Stata Corp., College Station, TX, USA).

2.5 Characteristics of Studies Included In the Meta-Analysis

Thirteen [9,10,20-30] studies met the inclusion criteria (see Fig. 1) and their characteristics are presented in Table 1. They all had satisfactory quality as shown in Table 2. The studies were from 6 countries in SSA: Uganda (4), South Africa (3), Nigeria (2), Zimbabwe (2), Kenya (1) and Congo (1). Among the studies 4 involved subjects off ART, 6 involved subjects on ART and 3 involved individuals on and off ART.

2.6 Characteristics of Individuals in the Included Studies

Individuals recruited in the studies consist of a mixed group of HIV asymptomatic and symptomatic infections (6), symptomatic patients only (3) and asymptomatic patients only (1). Two of the six studies that assessed Neurocognitive Impairment (NCI) used the International HIV Dementia Scale (IHDS) [21,22], one used Structured Interview Diagnosis of Dementia According to the DSMIV (SIDAM), another one used mental state examination [27] and two used Mini Mental State Examination (MMSE) {one of the studies found none of the HIV infected subjects having Neurocognitive Impairment (NCI)} [23]. None of the studies recruited subjects via mental health system or recruited subjects receiving anti-depressant drugs. Plasma viral load was not reported in all the included studies.

Table 1. Demographic and other characteristics of included studies

First author/ year	Country	Study design	Sample size	Interview/ Criteria	Mean age	Mean CD4 count	On ART (%)	Comments/ Sources of bias
Freeman 2007 [20]	S/Africa	C	900	CIDI/DSM-IV	NA	NA	18	Sample involved people in rural, semi-urban and urban areas.
Nakimuli-Mpungu 2011 [21]	Uganda	C	500	MINI/DSM-IV	40[a]	NA	100	Excluded debilitating illness, not TB. Done in rural setting. 64.2% had NCI on IHDS.
Kinyanda 2011 [22]	Uganda	C	618	MINI/DSM-IV	NA	NA	64.6	Excluded physically and mentally sick. 7.7% had NCI on IHDS.
Adewuya 2007 [23]	Nigeria	C	175	MINI/DSM-IV	40.23	NA	100	Excluded cofounders. Majority of subjects belong to low SES.
Sebit 2003 [24]	Zimbabwe	C	194	CIDI/DSM-IV	NA	51	Non	Excluded confounders. NCI assessed with MMSE.
Myer 2008 [25]	S/Africa	C	465	MINI/DSM-III R	33[a]	234[a]	48	Excluded NCI using MMSE.
Sebit 2002 [26]	Zimbabwe	P	22	CIDI/DSM-IV	36.4	NA	Non	Excluded confounders. Small sample size. No NCI on SIDAM.
Olisah 2010 [27]	Nigeria	C	310	SCAN/ICD 10	35.5	NA	100	Excluded NCI and other confounders.
Petrushkin 2005 [10]	Uganda	C	46	MINI/DSM-IV	36.6	NA	NA	Small sample size. Alcohol not excluded. 24% had TB.
Gaynes 2012 [28]	Cameroon	C	400	CIDI/DSM-IV	41[a]	NA	100	Done in single urban center.
Nakimuli-Mpungu 2012 [29]	Uganda	C	200	MINI	40.4	NA	100	MINI depression diagnostic section validated in Uganda.
Olley 2003 [30]	S/Africa	C	149	MINI	30	346.3	1.3	All cases were seeking treatment. Males older than females significantly.
Maj 1994 [9]	DR Congo	C	205	CIDI/DSM-III, ICD 10	33.5	415	Non	Major confounders not excluded.
Maj 1994 [9]	Kenya	C	203	CIDI/DSM-III, ICD 10	31.95	480	Non	Major confounders were not excluded.

[a] median, C-cross-sectional, CIDI- Composite International Diagnostic Interview, DSM- Diagnostic and Statistical Manual of Mental Disorders, IHDS- International HIV Dementia Scale, ICD- International Classification of Diseases, MINI- Mini Neuropsychiatric Interview, MMSE- Mini Mental State Examination, NA- Not Available, NCI- Neurocognitive Impairment, P-prospective, SCAN- Schedule for Clinical Assessment in Neuropsychiatry, SIDAM- Structured Interview Diagnosis of Dementia According to the DSMIV (SIDAM), TB- Tuberculosis

Table 2. Assessment of study quality using downs and black checklist [19]

Authors	Accrued from same population	Accrued same time period	Modest sample size	Comparator group	Addressed lost to follow-up	Reported baseline characteristics	Reported confounders	Reported measures to curtail bias
Freeman 2007 [20]	Y	Y	Y	N	NR	N	N	Y
Nakimuli-Mpungu 2011 [21]	Y	Y	Y	N	NR	Y	Y	Y
Kinyand 2011 [22]	Y	Y	Y	N	NR	Y	Y	Y
Adewuya 2007 [23]	Y	Y	Y	Y	NR	Y	Y	Y
Sebit 2003 [24]	Y	Y	Y	N	NR	Y	Y	Y
Myer 2008 [25]	Y	Y	Y	N	NR	Y	Y	Y
Sebit 2002 [26]	Y	Y	N	N	Y	Y	Y	Y
Olisah 2010 [27]	Y	Y	Y	N	NR	Y	Y	Y
Petrushkin 2005 [10]	Y	Y	N	N	NR	Y	Y	Y
Gaynes 2012 [28]	Y	Y	Y	N	NR	Y	Y	Y
Nakimuli-Mpungu 2012 [29]	Y	Y	Y	N	NR	Y	Y	Y
Olley 2003 [30]	Y	Y	Y	Y	NR	Y	Y	Y
Maj 1994 [9]	Y	Y	Y	Y	NR	Y	Y	Y

N = No; NA = Not Applicable; NR = Not Relevant; Y = Yes

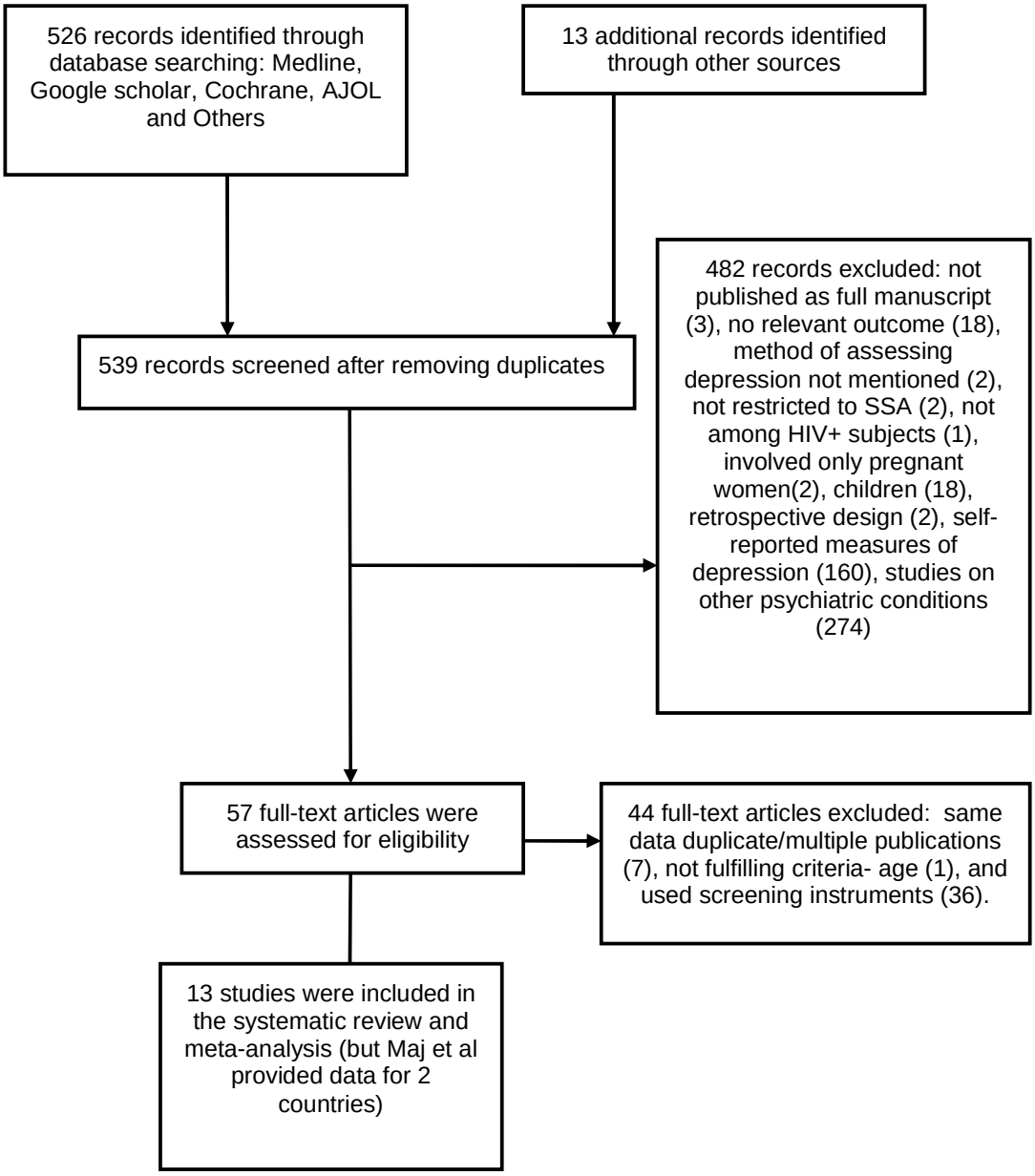

Fig. 1. PRISMA flow diagram of the process of article selection for the systematic review and meta-analysis

3. RESULTS FROM META-ANALYSIS

3.1 Prevalence of MDD

3.1.1 HIV- infected and HIV- negative subjects

The REM estimate of prevalence (95% CI) of MDD among HIV- infected subjects from all the 13 studies was 17.31% (11.65-22.97) as shown in Fig. 2. There was no publication bias (Begg's test, *P* value = .180; Egger's test, *P* value = .008). The prevalence of MDD based on the type of diagnostic interview was: MINI = 20.21 (10.51-29.91) and CIDI = 20.14 (11.07-29.21). For HIV-negative control subjects the prevalence of MDD from 3 studies was 4.0% (-0.02 to+0.10). No publication bias was observed (Begg's test, *P* value = 1.00; Egger's test, *P* value = .047).

3.1.2 Subjects on and off ART

The REM estimate of prevalence of MDD among subjects on ART from 5 studies was 9.76 % (4.63–14.89). There was no publication bias (Begg's test, *P* value = 1.00; Egger's test, *P* value = .117). The REM estimate of prevalence of MDD among subjects off ART from 5 studies was 15.97% (3.59-28.34). There was no publication bias (Begg's test, *P* value = .806; Egger's test, *P* value = .534). No significant difference in the prevalence between the two groups (Chi square = 1.58, *P* = .208).

3.1.3 Symptomatic and asymptomatic HIV-infected subjects

The REM estimate of prevalence of MDD among symptomatic (AIDS) HIV- infected adults from 6 studies was 17.50% (7.82-27.18). There was no publication bias (Begg's test, *P* value = .133; Egger's test, *P* value = .006). The REM estimates of prevalence of MDD among asymptomatic HIV- infected adults from 3 studies was 8.33% (-2.62 to+19.29). There was no publication bias (Begg's test, *P* value = 1.00; Egger's test, *P* value = .793). Symptomatic (AIDS) patients had significantly higher prevalence than asymptomatic patients (Chi square = 4.42, *P* = .0355).

3.2 Correlates of MDD

3.2.1 Medical conditions

When compared to HIV- negative subjects, the OR (95% CI) for developing MDD among HIV-infected subjects from 4 studies was 3.1 (1.97-4.17). There was no publication bias (Begg's test, *P* value = 1.00; Egger's test, *P* value = .314). Other medical correlates of MDD were AIDS (OR = 1.52, 95% CI = 0.8-2.88) and Tuberculosis (TB) (OR = 2.34, 95% CI = 1.0-5.63).

3.2.2 Sociodemographic factors

When compared to HIV- infected males, the OR (95% CI) for developing MDD among HIV-infected females from 3 studies was 1.71 (1.09-2.32). There was no publication bias (Begg's test, *P* value = .806; Egger's test, *P* value = .419). When compared to HIV- infected females, the OR (95% CI) for developing MDD among HIV- infected males from 3 studies was 0.85 (0.69-1.02). Other sociodemographic factors were rural residence (OR = 0.72, 95% CI = 0.29-1.81) and living > 5 kilometer away from HIV clinic (OR = 1.51, 95% CI = 0.56-4.07).

3.2.3 Specific society troubles for role assignation

From three studies the OR (95% CI) of having MDD among HIV- infected subjects with higher income compared to those with lower income was 0.68 (0.45-1.0). Other correlates of MDD each derived from 2 studies were high social support (OR = 0.75, 95% CI = 0.60-0.90), social stress (OR = 1.74, 95% CI = 0.63-4.81) and widowed/divorced (OR = 1.3, 95% CI = 0.90-1.96). Only one study assessed food insecurity in relation to MDD (OR = 2.89, 95% CI = 1.40-5.89).

4. DISCUSSION

In the current study the estimated prevalence of MDD from 13 studies involving HIV- infected subjects in SSA was 17% and is similar to the 18% derived from 6 studies previously [11]. However, a meta-analysis that included studies worldwide found 9.4% prevalence of MDD among HIV- infected subjects which sharply contrast to the finding in this meta-analysis [31]. The devastating effects of HIV infection in SSA and the fact that the region has more than two-thirds of the global burden of HIV- infection in the world coupled with low ART coverage could account for the higher prevalence observed in this study. Other factors contributing to the high prevalence of MDD among HIV- infected individuals in SSA include late presentation of patients with advanced disease, lower CD4 count and high viral load. These biomarkers of disease are closely related to MDD among HIV- infected individuals [6-7].

This meta-analysis found no significant difference in the prevalence of MDD in terms of ART utilization. Differences in ART regimen, Central Nervous System (CNS) penetration effectiveness (CPE) of the individual drugs and level of ART adherence could account for the non-significant difference in the prevalence of MDD between subjects on and off ART. Symptomatic patients with AIDS had significantly higher prevalence of MDD as compared with asymptomatic patients in this study and contrast with previous reports that found no significant difference between the two groups [31]. It is imperative to note that this meta-analysis was

restricted to SSA, the region with the highest prevalence, burden, morbidity and mortality of HIV/AIDS in the world [32]. Symptomatic individuals with advanced disease, AIDS, opportunistic infections (including TB) and NCI may experience more symptoms of depression than asymptomatic individuals. It has been observed that symptoms of depression may start rising about 1 year before AIDS diagnosis and usually peaked and plateau around 6 months prior to AIDS diagnosis [33]. The rate of development of AIDS is significantly faster among HIV- infected patients with MDD when compared with those without MDD [34,35]. Also the risk of progression to AIDS is doubled for each severe symptom or with every 3-point increment in depression score [36]. Other factors that contribute to disease progression are stress and social support which are associated with 2 to 3 times higher risk of progression to AIDS when compared to those with less stress and better social support [36]. Each unit decrease in social support point is associated with a nearly 3 times increased risk of progression to AIDS stage [36].

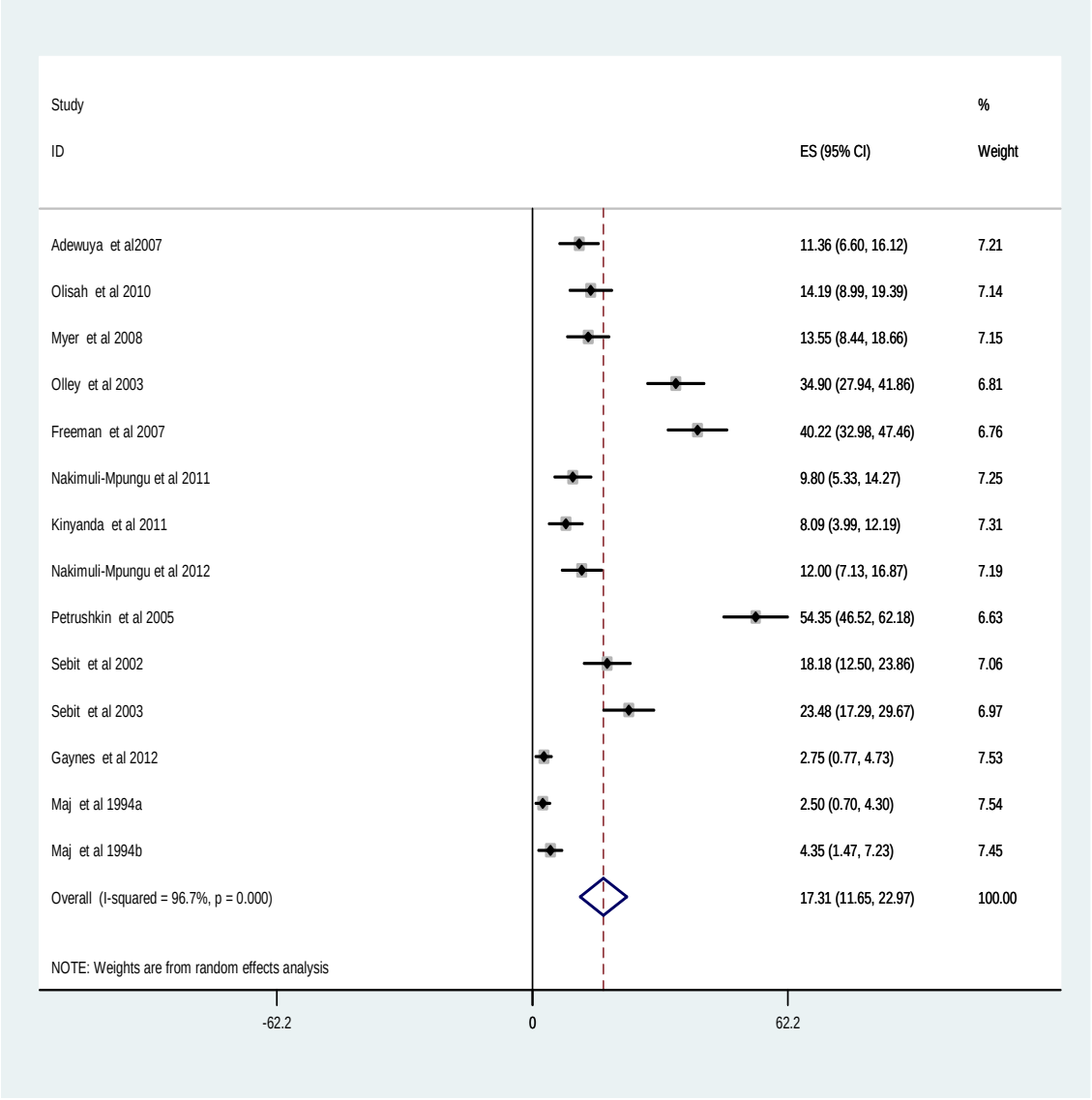

Fig. 2. Forest plots of the meta-analysis of the prevalence of MDD among HIV- infected patients in SSA. This figure showed the pooled estimate of prevalence of MDD among patients on and off ART

Female gender has been found to be associated with more symptoms of depression, higher morbidity and mortality than male gender [37]. In a 7 year longitudinal study it was found that HIV-infected women with chronic depressive symptoms were twice more likely to die compared to those with limited or no depressive symptoms after controlling for confounders [38]. Globally women constituted half the adults living with HIV and the burden of HIV on women is heaviest in SSA [39]. Economic dependence on male partners, low SES, low educational level, under utilization of health services and the pressure of caring for the children also contribute to the higher risk of depression among female HIV- infected subjects [37].

One of the limitations of this meta-analysis is that estimates from this study were derived from studies conducted only in SSA and may not apply to other regions of the world due to differences in epidemiology of HIV infection, viral diversity, SES, access to ART and other healthcare services. Also not all the studies excluded subjects with other psychiatric diseases, substance abuse, alcohol, NCI and co-morbid medical illnesses which are confounders and potential sources of heterogeneity. Specifically triple diagnosis (HIV infection, mental illness and substance abuse) could be a potential confounder [40]. Although we have included studies diagnosing MDD based on MINI and CIDI, separate estimates were in sub-group analyses of studies with these two diagnostic methods similar. Strength of this meta-analysis is the inclusion of studies that utilized diagnostic interview for assessment of depression thus avoiding the confounding effect of somatic symptoms of HIV infection. The inclusion of subjects not recruited via the mental health system reduces selection bias thereby increasing reliability and accuracy of derived estimates.

5. CONCLUSION

The prevalence of MDD among HIV- infected subjects in SSA is higher than the prevalence reported from other parts of the world. Symptomatic patients with AIDS have significantly higher prevalence than asymptomatic patients. HIV infection, TB, female gender, food insecurity, income and social support are important correlates of MDD that could help in designing screening and targeted intervention among HIV- infected subjects in SSA. We recommended that more efforts should be made to avoid progression of HIV to AIDS stage and improving the social welfare of these patients needs to be given special attention. Routine care of HIV/AIDS patients should incorporate assessment and therapy for MDD. Given the huge burden of HIV/AIDS and MDD in SSA, HIV preventive practices need to be emphasized. These include use of condoms, avoiding risky sex, limiting number of sexual partners and avoiding intravenous drug usage among others. Alcohol ingestion could potentially dampen the positive impact of these preventive strategies and should be avoided. For subjects already infected with HIV, prevention and treatment of MDD could help reduce the transmission and spread of HIV.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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