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Effectiveness of Depression Interventions for People Living with HIV in Sub-Saharan Africa:**A Systematic Review & Meta-Analysis of Psychological & Immunological Outcomes**

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ABSTRACT

This meta-analytic review evaluated the effectiveness of depression interventions on the psychological and immunological outcomes of people living with HIV in sub-Saharan Africa. 14 studies, yielding 932 participants were eligible. A random-effects models indicated that depression interventions were followed by large reductions in depression scores (effect size = 1.86, 95% CI = 1.71, 2.01, $p < 0.01$). No significant effect on immune outcome was observed, however there was a trend toward immune improvement of medium effect size (effect size on CD4 count and/or viral suppression = 0.57, 95% CI = -0.06, 1.20, $p = 0.08$). Pharmacological interventions appeared to have a significantly larger improvement in depression scores than psychological interventions. The greatest improvement in immune status was demonstrated in psychological treatments which incorporated a component to enhance HIV medication adherence, however these results did not reach significance. Small sample sizes and highly heterogeneous analysis necessitate caution in interpretation. The results of this meta-analysis should thus be treated as preliminary evidence and used to encourage further studies of immunopsychiatry in HIV in sub-Saharan Africa.

Keywords

CD4; depression; HIV/AIDS; immunopsychiatry; intervention; meta-analysis; psychoneuroimmunology; review; sub-Saharan Africa; viral load

1. INTRODUCTION

Sub-Saharan Africa is the centre of the HIV epidemic, with nearly 26 million people (69% of the global burden) estimated to be infected [1]. Improved access to antiretroviral therapy (ART) [1] is associated with the 34% increase in life expectancy in sub-Saharan Africa over the past 15 years [2]. However, the change in prognosis has revealed vast challenges of this chronic disease endemic in resource limited populations. Major depressive disorder (MDD) is the most common psychiatric manifestation associated with HIV infection [3], and one of such challenges. It is twice as common in people living with HIV as in general populations [4, 5], with a prevalence of up to 36% [6-8], and a treatment gap estimated to be as high as 90% in low and middle income countries[9].

The primary aim of this systematic review and meta-analysis was to evaluate the effectiveness of depression interventions on the psychological and immunological outcomes of people living with HIV in sub-Saharan Africa. The secondary aim was to assess which types of interventions appear to have the largest effect on depression and immunological outcomes.

1.1 Aetiology of Major Depressive Disorder in People living with HIV

Psychological, social and biological factors are all implicated in the aetiology of MDD in HIV[10]. Psychosocial risk factors identified in the sub-Saharan African population include: female gender, older age, unemployment, negative life events, childhood trauma, disability and impaired function, poor social support, low quality of life, life-time attempted suicide, and associated psychiatric illness [10, 11].

The biological aetiology of MDD in people living with HIV is linked, at least in part, to the pro-inflammatory cascade driven by the HIV infection [12, 13]. Rivera-Rivera et al demonstrated a broad panel of pro-inflammatory cytokines in the plasma of individuals with HIV and depression symptoms compared to their non-depressed counterparts [14]. In animal models, a single exposure to HIV Tat-protein in the mouse brain induces brain cytokines signalling of IL-1 β , TNF- α , and IL-6, which culminates in depressive-like behaviour [15]. Similarly, elevated levels of IL-1 β , IL-6, and TNF- α have been identified in both the plasma and cerebrospinal fluid of depressed patients [16]. The rise in these cytokine levels are thought to induce the sickness behaviour which manifests as depression in people with HIV [13].

1.2 The Effect of Major Depressive Disorder on Immunity

The biological pathways of MDD itself can contribute to low immunity, and increased mortality in people living with HIV [17]. For example, MDD and distress states associated with MDD, influence the regulation of stress hormones, such as cortisol and catecholamines, decreasing pro-inflammatory (anti-viral) immunity [18] while increasing anti-inflammatory immunity [19]. This can lead to alterations in the function and/or number of lymphocytes and natural killer (NK) cells [18, 20-22], and enhance HIV replication [23]. As a result, dual diagnosis patients with HIV and MDD may have increased rates of progression to advanced stages of disease [13, 24, 25].

Furthermore, symptoms of MDD such as impaired concentration, memory, problem-solving and motivation [26] can result in negative HIV related behaviours. Most notable of these, is a delay in initiating [27], and impairment in adhering to, ART [28, 29]. However, poor mental

health predicts faster HIV disease progression even after controlling for adherence [30] and is independently associated with increased HIV mortality [17, 30, 31].

1.3 Management of Major Depressive Disorder in People Living with HIV

The cornerstone of MDD management in people living with HIV is psychopharmacologic treatment using antidepressants [32]. Selective serotonin reuptake inhibitors (SSRI) are first-line due to their efficacy and minimal adverse effects [33]. SSRI treatment may have a direct immunomodulatory effect [34] [35, 36], since serotonin (5-hydroxytryptamine [5-HT]) receptors and the 5-HT transporter are found on monocytes, macrophages, T cells, and possibly NK cells [37]. By downregulation of HIV receptor and co-receptor expression on these immune cells, treatment with SSRI may reduce susceptibility to cellular infection [34] [38].

In contrast, psychological modalities for treatment are recommended as the first-line intervention by the WHO's Mental Health Gap Action Programme (mhGAP) [39]. In a global review by Sherr et al, of 90 interventional studies for depression in people living with HIV, psychological interventions were assessed to be generally more effective than pharmacological treatments [40] in reducing depression. Furthermore, evidence suggests that psychological interventions for people living with HIV may improve immune status by modulating the associated neuroendocrine pathways [20]. Animal and human studies have demonstrated that stress accelerates HIV-1 disease pathogenesis and impairs the biological impact of ARV treatment [41].

In summary, multiple pharmacological and psychological interventions for depression have been evaluated for people living with HIV, with some studies also assessing the impact of treatment on immune measures. However, to date the majority of reviews of depression

studies for people living with HIV have reported on the population of white males, from the United States (US) or Europe [40]. There has not been a systematic review and meta-analysis examining which treatment modalities result in the most significant improvements in both depression and immune status in the sub-Saharan Africa population, where most HIV patients are.

2. METHODS

2.1 Data Sources

Relevant studies were identified by searching the electronic databases: MEDLINE, EMBASE, PsycINFO, and The Cochrane Library. All searches were conducted on 27 July 2016 and no limits were applied. The search terms (Appendix 2) reflected four categories: (1) HIV/AIDS, (2) Depression, (3) Intervention, and (4) Sub-Saharan Africa. Experts and authors in the field of depression in people living with HIV in sub-Saharan Africa were contacted and asked to respond with any missing literature. A hand search of reference sections from relevant articles was conducted and 'grey literature', including conference abstracts, was explored using OpenGrey and WorldCat databases. A repeat search was performed in Pubmed on 5 March 2018 with no relevant new studies found.

2.2 Study Selection

Published and unpublished studies (in any language) were included in the systematic review if they met all 4 of the following criteria: (1) described an intervention aimed at reducing depression in people living with HIV, (2) targeted individuals 18 years of age or older, (3) set in Sub-Saharan Africa and (4) reported outcome data on pre- and post-intervention depression outcomes as a score rating, with or without immunological data. Studies included in the meta-analysis, additionally, required that the mean and standard deviation

of pre- and post-intervention total outcomes, or sufficient information to calculate this, was available.

Participant populations with a specified comorbidity (e.g. drug abuse) as well as perinatal studies, were excluded since this would introduce external physical factors. As this analysis compares change scores within groups, both ART treated and ART naïve patients were included. Research studying the initiation of ARTs was excluded due to expected significant immune status improvement.

2.3 Data Extraction

Studies from the electronic databases, grey literature and hand searching were exported into reference manager, EndNote [42], where duplicates were removed. Study title, abstract and text screening was performed, repeated by a second author (IE), and discrepancies reconciled via discussion. From the selected studies, information was extracted using standardised abstraction table.

2.4 Quality Assessment

The Cochrane Collaboration's Tool for Assessing Risk of Bias [43] was used to assess level of quality and corresponding levels of bias in each study. This tool assesses methodologic quality variables of random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective reporting and other bias.

2.5 Analytic Approach

2.5.1 Outcome Variables

We found that most studies had used more than one instrument to measure immunological and/or depression outcomes (see Table 1 and Table 2). To reduce the measurement variance and optimize the comparison of outcomes, we chose to analyse the instruments used most frequently across studies. For depression outcomes, these were the Beck Depression Inventory-II, Patient Health Questionnaire-9, Self-Reporting Questionnaire-8, and the Hamilton Depression Scale. For immunological outcomes, these were CD4 count and viral suppression. Due to the large variation in intervention time frame and follow up, we analysed the first time point as the outcome, compared to the baseline measure.

2.5.2 Effect Size Calculation

In two separate analyses, the mean immunological and depression outcomes pre- and post-intervention were used to calculate a change-from-baseline effect size (ES) also known as the Standardized Mean Difference (Cohen's d [44]) (*Appendix 3*). Only the 'change scores' from the interventional arm were analysed. For this, a version of the Cohen's d calculation known as the Standardised Mean Gain (SMG) was used to calculate ES. The 'change score' approach is recommended when participants are not all randomised (Higgins et al., 2011) or for studies with small sample sizes, which are susceptible to baseline imbalances [45]. The method is well suited for this review, as a comparison of outcomes could be made without the need for a control group to be present in every study.

The ES for depression outcomes were calculated from continuous variables (depression score), while immunological outcomes were both dichotomous (viral suppression) and continuous (CD4 count). Immune outcomes were first analysed in separate outcomes of CD4 and viral suppression, before being combined into a unified immune outcome. The ES of

dichotomous data from viral suppression was converted to continuous data (see calculation in Appendix 3) to allow for combination with CD4 count change scores.

The corrected effect size was calculated using Hedge's g to produce an unbiased [46] final result. By convention, a positive sign is assigned to the effect size when there is improvement from pre- to post-intervention (i.e. the bigger the change from baseline, the better the outcome). A negative sign is assigned when the effect is in the opposite direction.

2.5.3 Cochrane Collaboration Review Manager 5

Data calculated was then entered into Cochrane Collaboration Review Manager 5 [47] for meta-analysis. A weighted effect size for each study is generated (i.e. inverse variance) using Hedges formula [48] based on the standard error (SE) of each ES. The I^2 statistic was chosen to calculate the degree of statistical heterogeneity because of the small number of studies [49]. Since heterogeneity was high between studies, a random effects model was used. This generates a conservative estimate of variance providing more generality [50].

2.5.4 Stratified Analysis

Stratified analyses of depression and immune outcomes was performed to examine whether intervention characteristics moderated the strength of the aggregated effect size.

Once the most common treatment groups were identified, we compared the aggregated effect sizes. The subgroups between-group heterogeneity was calculated using the I^2 statistic and the test for subgroup differences was done using the Chi^2 statistic.

Due to the large variation in intervention types, wide-ranging treatment subgroups had to be identified. A comparison of pharmacological vs non-pharmacological was the broadest, and most logical, subgroup category. Delivery methods, ARV status, treatment location and

duration, and antidepressant drug groups were considered for stratified analysis, but not conducted, due to lack of information on these factors, or wide varieties (e.g. five different antidepressants), making a comparison number within subgroups too small to assess.

3 RESULTS

3.1 Study and Sample Characteristics

As shown in the PRISMA Flow Diagram (Appendix 1), 14 articles were deemed eligible for review. Of these, 13 studies had sufficient information to be included in the meta-analysis for depression outcomes and five for immunological outcomes, totalling 932 participants. Data abstraction (Table 3) showed studies took place from 2006-2016 in Sub-Saharan African countries, namely South Africa, Nigeria, Uganda, Tanzania, Zimbabwe, and Cameroon, with the majority in South Africa (43%). Majority of interventions were set in HIV clinics or HIV day clinics within a hospital (57%). The largest study sample size was 184 participants [51] and the smallest was 9 [52]. The majority of participants were female (73%) with age range of 21-56 years. Most studies (57%) included only patients known to be on ART. The remaining studies included mixed ART and non-ART patient samples or did not specify the ART status. Three studies (21%) had patients known with poor adherence at baseline.

3.2 Intervention Characteristics and Components

Study designs were: 36% randomised control trials, 14% non-randomised control trials, and 50% interventional trials without a control arm. Half of the studies used a pharmacological approach. Both selective serotonin reuptake inhibitors (Escitalopram, Citalopram, Fluoxetine) and tricyclic antidepressants (Amitriptyline and Imipramine) were prescribed. One study (Moosa et al, 2012) compared and independently reported results from a

pharmacological and non-pharmacological intervention within the same study. Results from both arms of this study were analysed separately in the stratified analysis, to avoid over-representation. The components of psychological interventions varied extensively. Problem-solving therapy and cognitive behavioural therapy were most commonly used psychological interventions (28%). Psycho-education, interpersonal therapy, and art psychotherapy were used for the remaining interventions. Task-shifting was the most common delivery approach (57%) across all interventions. In this model, tasks normally performed by a physician are transferred to a health professional with a different or lower level of education and training, or to a person specifically trained to perform a limited task only without having formal health education [53]. The remaining studies (43%) used medical officers, a stepped-care model, or did not specify. All pharmacological treatment was received as a daily dose. The median number of non-pharmacological intervention sessions was 6 (range: 1–8 sessions). The median intervention duration was 12 weeks (range: 4 – 24 weeks).

3.3 Methodologic Quality of Studies

Random sequencing, allocation concealment and blinding was lacking or unclear in over 75% of studies. From the six studies with the highest levels of bias, majority (four) were pharmacological interventions [51, 54-56] and two were non-pharmacological studies [57, 58]. Attrition bias was low (21%), with most studies having small dropout rates, and giving clear explanations thereof. Reporting bias was also low, as 100% of studies state clearly the aim and outcomes being examined. With majority of studies being non-RCT trials (64%), the lack of random assignment and a placebo control groups, results in a generalized poor level of quality.

3.4 Effect Size Analysis of Depression & Immune Outcomes

3.4.1 Depression Outcomes

Analysis of depression outcomes revealed a large aggregated ES reflecting the magnitude of change from pre- to post-intervention and providing strong evidence for post-intervention improvement in depression (SMG = 1.86, 95% CI = 1.71, 2.01; $p < 0.0001$). Two studies contribute to the majority of the weight of the analysis: Peltzer et al, 2012 and Ngo et al, 2015 (Figure 1).

Figure 1: Forest Plot Depression Outcome Change Scores

3.4.2 Immune Outcomes

Three out of the four studies reporting CD4 count, showed an improvement post-intervention (Figure 2.1). However only one showed a significant ES [59]. The one study eliciting a negative effect on CD4 outcome had a non-significant result [60]. The overall effect was in the direction of favouring post-treatment improvement in CD4 count, but the ES was small (SMG = 0.15, 95% CI = -0.15, 0.44, $p = 0.33$) and failed to reach statistical

significance.

Figure 2.1: Forest Plot Immune Outcome Change Scores (CD4 Count)

Results from the three studies using viral suppression as an outcome, indicate that the odds of being virally suppressed are four times greater post-treatment of depression. However, the final effect, although favouring post-intervention with a medium ES, had wide confidence intervals and just failed to reach statistical significance. (OR = 4.00, 95% CI = 0.82, 19.49, $p = 0.09$) (Figure 2.2).

Figure 2.2: Forest Plot Immune Outcome Change Scores (viral suppression)

Combining of immune outcome CD4 count and viral suppression, showed post-intervention immune improvement (Figure 2.3). This analysis provides a narrow 95% CI (-0.06; 1.20), but

the final result just crosses the line of no effect, showing a medium effect size (SMG = 0.57), and trend-level statistical significance ($p = 0.08$).

Figure 3.1: Forest plot showing the Standardized Mean Difference (IV, Random, 95% CI) for five studies (Abas et al., 2015; Gaynes et al., 2015; Hoare et al., 2014; Nyamayaro et al., 2016; Peltzer et al., 2012).

Between study heterogeneity accounted for over 90% of variance in the ES of both depression and immune outcomes, indicating that, although favouring the same direction of effect, diversity between studies is extremely high reflecting the combined construct measures.

3.5 Stratified Analysis

3.5.1 Non-Pharmacological versus Pharmacological Interventions

3.5.1.1 Depression Outcomes

Although both pharmacological and non-pharmacological treatments show significant improvement in depression outcomes post-intervention, the ES of pharmacological treatments is more than double the ES of non-pharmacological treatments. Thus, there was a large and significant subgroup difference ($\chi^2 = 10.21$, $df = 1$, $p < 0.01$) favouring pharmacological intervention improvement in depression scores (Figure 3.1).

Figure 3.1 : Forest Plot Depression Outcomes : Non-Pharmacological Vs Pharmacological Interventions

3.5.1.2 Immune Outcomes

Neither pharmacological nor non-pharmacological interventions show significant immune effects independently. The pharmacological interventions who reported immune outcomes (two studies both using CD4 count outcomes) have, if anything, a negative effect on immunity, however, this result shows a minute effect size, with no significance (SMG = -0.06, 95% CI = -0.29, 0.18, $p = 0.64$). In contrast, non-pharmacological interventions (three studies, two of which used CD4 count outcomes, and one using viral suppression as an outcome) show a trend towards immune improvement with a large but non-significant effect size (SMG = 1.02, 95% CI = -0.19, 2.24, $p = 0.10$). The effects of the interventions are in opposition, making the resulting subgroup difference between interventions large ($\text{Chi}^2 = 2.29$, $\text{df} = 1$). However, the small comparison yields a non-significant ($p = 0.09$) result (Figure 3.2).

Figure 3.2 : Forest Plot Immune Outcomes : Non-Pharmacological Vs Pharmacological Interventions

4. DISCUSSION

This study is the first systematic review and meta-analysis of depression interventions for people living with HIV in sub-Saharan Africa. It demonstrates improvements in both mental health and immune status with varying levels of clinical and statistical significance.

4.1 Depression Outcomes

The findings in this study are in keeping with a previous systematic review of depression interventions for people living with HIV, in mainly high-income countries [40], with most interventions being statistically effective in reducing depression. However, contrary to the findings by Sherr et al, which showed psychological interventions to be more effective than pharmacological interventions, our study found that antidepressant treatment was more effective than psychological interventions in the reduction of depression scores. This could suggest that psychotropic treatments for depression could be more effective and offer better outcomes in a sub-Saharan Africa population. However, these findings need to be confirmed in larger samples or future systematic reviews.

The variation in treatment response might be explained by ethnic differences between this study populations and previous studies with majority European/American populations. For example, genetic profile has been shown to predict better antidepressant outcomes in an ethnicity-dependent manner [61]; however, another study found no significant differences between White and African-American MDD patients in their response to pharmacological versus psychological treatments [62]. Of course, the use of Western-developed psychological treatments in an African setting could explain the less significant improvement in our meta-analysis; indeed, Griner et al suggest that mental health treatments should be modified to better match cultural context, with a meta-analysis indicating a moderately

strong benefit of culturally adapted interventions on depression outcomes [63].

Alternatively, delivering high quality psychological treatments may be difficult in the context of sub-Saharan Africa where facilities and trained psychologist are limited. In fact, the majority of the studies using psychological treatment in our meta-analysis recruited lay health workers to deliver the intervention (6 of 8 studies) whereas a much smaller proportion of the pharmacological interventions were delivered by lay health care workers (3 out of 7); and psychosocial informational interventions may require more advanced skill training in lay health workers to achieve superior outcomes in this resource-constrained setting [59]. Furthermore, within our meta-analysis, studies using pharmacological interventions had, on average, a longer treatment duration (mean 14 weeks) compared to studies using a non-pharmacological intervention (mean 10 weeks). Successful treatment of depression, in both pharmacotherapy and psychotherapy treatment, relies heavily on provider contact to be effective [64]. Discrepancies in treatment duration is thus a possible confounder of these results. Lastly, the majority (5/8) of pharmacological intervention studies were assessed to have high levels of selection, performance and/or detection bias, thus results should be treated with caution. We can only speculate the reasons for the greater success of pharmacological depression treatment in this setting, and further research is required to better explain this finding.

4.2 Immunity Outcomes

Five studies measured both depression and immune outcomes, but the correlation between improvement in depression and immune outcomes was not tested statistically in any of the papers. However, the relationship between improvement in depression and immune outcomes was discussed briefly by two individual papers in this review [6, 59]. Gaynes et al

emphasized that this finding is consistent with a model in which effective depression care yields improved HIV outcomes [6].

In the meta-analysis, no significant immunological improvements were observed in either the psychological or pharmacological treatment arms. This finding is endorsed by a meta-analysis of cognitive-behavioural interventions, by Crepaz et al, which showed significant intervention effects on symptoms of depression ($d = 0.33$) but limited evidence suggesting effects on CD4 cell counts ($d = 0.08$) [65]. Similarly, two recent, randomized trials of medication-based depression treatment in the US showed no effect on HIV outcomes [66, 67]. In the first study, fluoxetine significantly improved depression but with no statistically significant differences in secondary HIV outcomes between intervention and control arm [66]. In the second study, the largest trial of its kind among HIV-infected adults, a three-year medication based depression treatment did not improve HIV outcomes but achieved clinically significant depression improvements. Notably, these results were thought to be due to high baseline ART adherence in this study population [67].

However, the trend towards immune improvements, particularly demonstrated by psychological interventions, in this review are also in keeping with research in the field. Two RCTs, one providing cognitive-behavioural stress management [68] and another mindfulness meditation training [41], demonstrated an increase in NK cells and CD4+ T-cells ($b = 106.27$, $SE = 56.89$, $t [66] = 1.87$, $p = .06$), together with evidence of a buffered CD4+ T lymphocyte decline ($b = .014$, $t (74) = 2.09$, $p = .04$), respectively. International studies, in the US, using antidepressant treatment have similarly shown a trend toward improvement in immune status. A prospective cohort study in California showed that treatment with antidepressants (non-specified) resulted in double the odds of achieving viral suppression (95% CI, 1.15-

3.58; $P = .02$), and nearly doubled the odds of achieving complete adherence to ART (weighted OR, 1.94; 95% CI, 1.20-3.13; $P = .006$) [69]. Another cohort study found that among depressed patients, those compliant with SSRI had improved ART adherence and statistically greater increases in CD4 cell responses [70]. Furthermore, the CHARTER cohort HIV study reported that individuals taking SSRIs were more likely to have lower HIV viral loads in cerebrospinal fluid and better neuropsychological performance [71].

4.3 Effects of ART Adherence

It is important to note that the psychological treatments included in the meta-analysis all had an adherence component incorporated into the intervention. It is well established that depression in people living with HIV is significantly associated with non-adherence to ART [72]. A recent South African study demonstrated that patients reporting non-perfect adherence were approximately three times more likely to have moderate to severe symptoms of depression than those reporting perfect adherence [73]. After treatment for depression, a meta-analysis by Sin et al [74] has showed that the odds of a person adhering to ART were 83 % better. The resulting immune improvements in depression treatment are thus thought to be primarily mediated through the increased ART adherence when being treated for depression [70, 75]. Relationships between immunity, depression, and adherence appear to be closely intertwined

The lack of immune improvement seen with primarily psychotropic interventions in this review tentatively suggests that treatment modalities relying solely on antidepressants might not be addressing the underlying issues associated with non-adherence in lower-middle income setting of sub-Saharan Africa. Adherence counselling within depression management in this research and others discussed above, appears to be a necessary and

successful component of treatment, which indirectly improves immune outcomes. In the context of sub-Saharan Africa, perhaps this should be considered an essential requirement in mental health policy. However, these findings are derived from a very small body of evidence and did not reach statistical significance, making evidence preliminary. Whether or not non-pharmacological interventions also improve immune outcomes through additional brain-body connection mechanisms is difficult to assess in this context, and might be better understood if future studies use a homogeneous population of people living with HIV already adherent to ART medication. Future research in the field might help further identify and promote the most effective methods of improving both mental and physical health for this population.

4.4 Limitations

In terms of methodological limitations, the studies in this review were generally of low quality and small sample size. The limited number of studies necessitated the inclusion of non-RCT trials in the meta-analysis, which can compound the biases present and generate misleading results [76]. There were insufficient studies to examine the effects of individual study characteristics (i.e. moderators and confounders) on the effect sizes. This could substantially contribute to better understanding factors underlying the effectiveness of different intervention groups. Comparing two different methods of treatment interventions can result in high levels of heterogeneity. Although sub-group analysis attempted to group similar treatments, there still exists high heterogeneity in sample size, time frame and study design, which calls for caution in interpretation since results being compared were very different in nature.

5. CONCLUSION

The evidence provided in this paper confirms that depression interventions are effective in the treatment of depression for people living with HIV in sub-Saharan Africa. However, the most effective treatment modalities for depression in people living with HIV in sub-Saharan Africa may differ compared with Western countries. Most notably, pharmacological treatment demonstrated a significantly larger improvement in depression score than psychological treatment modalities. These findings, however, are derived from a small body of poor quality research and should thus be treated as preliminary evidence only. Weak evidence exists for the effects of depression intervention on immune status in this population. Future research in sub-Saharan Africa ought to invest in methodologically sound RCTs to allow data collected to be meaningfully interpreted. Furthermore, mental health research could benefit from a broader collection of physical health outcomes to permit better understanding and advances in the field of psychoneuroimmunology.

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Conflicts of Interest

None known

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Table 1: Depression Outcomes Measures

Depression measure	Study
BDI-II	Olley 2006; Peltzer et al., 2012; Field & Kruger 2008
PHQ-9	Abas et al., 2016; Ngo et al., 2015; Petersen et al., 2014; Gaynes et al., 2015; Wagner et al., 2014; Pence 2014; Adams et al., 2012
SRQ-8	Abas et al., 2016; Nyamayaro et al., 2016
HAM-D	Hoare et al., 2014; Moosa & Jeenha 2012;
MADRS	Hoare et al., 2014;
HSCL-25	Petersen et al., 2014
SCID-I	Moosa & Jeenha 2012;
CESD-R	Andersen et al., 2016

Table 2: Immune Outcome Measures

Immune measure	Study
CD4 count	Peltzer et al., 2012; Ngo et al., 2015; Gaynes et al., 2015; Wagner et al., 2014; Hoare et al., 2014; Adams et al., 2012; Nyamayaro et al., 2016; Pence et al., 2014
CD8 count	Hoare et al., 2014
HIV RNA viral suppression	Abas et al., 2016; Gaynes et al., 2015; Nyamayaro et al., 2016
HIV RNA viral load	Gaynes et al., 2015; Pence et al., 2014

Table 3: Data Abstraction

Author(s), Year, Country	Participants: Sample size (N): Intervention (I) Control (C) Gender (M/F) Age (SD/range) ART Status Depression status	Intervention: Study type, intervention, control, setting	Delivery: Number of sessions, duration of intervention	Outcomes Measured:	Depression outcomes used in review:	Immunological outcomes used in review: Intervention (I) Control (C)	Result summary	Risk of Bias: The Cochrane Collaborati on's tool for assessing risk of bias Low(L) Unclear(U) High(H)
1. Peltzer et al., 2012 KwaZulu- Natal, South Africa	N= 152 I= 76 C= 76 M =53 F =99 Age = 36.9 SD=9.5 6-24 months on ART treatment with	Randomised control trial Intervention: Manualised cognitive behaviour group adherence intervention Lay health worker/adherence counsellor led	Sessions = 3 (1/month) Duration of intervention = 3 months	Adherence CD4 count Beck Depression Inventory II-total out of 63points, >20 depression	BDI ANOVA= 0.018 (p=0.894) I= baseline 26.8 (SD 22.2) f/u 19.7 (SD 19.3) Change: -7.1 C= baseline 25.5 (SD 23) f/u= 19.2	CD4 count ANOVA= 0.675 (p=0.412) I= baseline 308 (SD 217) FU 384 (SD 186) Change= 76 C= baseline 264 (SD 170)	Both treatment and control arms show improvements in immune and depression outcomes. Better immune outcomes in control arm. No significant	Selection: L/U Performance : U Detection: U Attrition: L Reporting: L Other: L

	adherence problems All patients scored as depressed on baseline BDI but not specified as in inclusion criteria	Control: Treatment as usual ART Clinic		Measured at baseline, month 1 and month 4	(SD 17.4) Change: -6.3	F/U= 368 (SD 196) Change= +104	difference between intervention and control conditions.	
2. Nyamayaro et al., 2015 Harare, Zimbabwe	N = 32 I= 14 C= 18 M= 11 F= 21 Age= 37.8 (24.6-44.9) On ART > 6 months with risk of poor adherence Mild depression at baseline assessed by PHQ-9>9	Two-arm pilot randomised controlled trial Problem-Solving therapy combined with Adherence counselling using a stepped care approach Lay health worker/adherence counsellor led Hospital Family Care Centre, government clinic	Sessions= 6 Duration of intervention = 8 weeks	Viral load (detectable viral load >200 copies/ml) Patient Health Questionnaire for depression Shona Symptom Questionnaire for common mental disorders Adherence	PHQ9 I: baseline 13.8 (SD 2.2) F/U 3.1 (SD 3.1) Change: 10.8 (95% CI 12.9, 8.8) C: baseline 9.2 (SD 3.3) F/U 5.7 (SD 3.9) Change: 3.4 (95% CI 5.8, 1.4) Intervention change (adjusted for baseline): 4.7 points lower (95% CI -8.2, -1.3 p=0.010)	Viral suppression I : baseline 7.1% ; F/U: 75% Change : 67.9% C : baseline 5.6% ; F/U 50% Change : 44.4% Data missing from (38% of participants)	Greater improvement in immune and depression outcomes in treatment arm after controlling for baseline scores	Selection: L Performance : H Detection: L Attrition: L Reporting: L Other: L

3. Hoare et al., 2014 Stellenbosch, South Africa	N = 102 I= 51 C= 51 M= 12 F= 90 Age =34 (23-56) ART: not specified Major depressive disorder at baseline assessed DSM-IV MINI-international neuropsychiatric interview-plus	Fixed-dose, placebo- controlled, semi- randomized, double-blind (convenience sampling) Escitalopram 10mg PO OD Delivery and monitoring not specified Hospital based intervention	Duration of intervention = 6 weeks Daily dose	Montgomery- Asberg depression rating scale Hamilton depression rating scale CD4 count CD8 count	HAM-D= I: baseline 21.3 (SD 5.2) F/U: 12.3 (SD 1.0) Change: -9 C: baseline 19.6 (SD 5.5) F/U: 11.8 (SD 8.4) Change: -8 Treatment difference: 1.1 (SE 1.7) (p=0.98)	ANCOVA model CD4 I: baseline 454.3 (SD 29.5) F/U 433.6 (SD 214.9) Change: -10.9 C: baseline 404.1 (SD 218.5) F/U 436.8 (SD 210.6) Change:43.3 Treatment difference: -54.0 (SE 35.6) (p=0.2)	Depression scores improved significantly in both intervention and control arm, however no significant advantage for Escitalopram over placebo. Better immune outcomes in control arm and worse immune outcomes in intervention arm (nonsignificant)	Selection: L Performance : L Detection: U Attrition: L Reporting: L Other: L
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4. Petersen et al., 2014 KwaZulu- Natal, South Africa	N= 76 I= 41 C= 35 Analysis N= 17 (high dropout) M= 50 F= 25 Age= (range only) 2i-59 On ART Major depressive disorder at baseline assessed by SRQ- 20	Randomized controlled trial Group-based IPT counselling intervention using a task shifting approach Delivered by HIV clinic counsellors HIV clinic	Duration of intervention = 3 months Number of sessions= 8	PHQ-9 HSCL-25 Hopkins symptoms check list	PHQ-9 I: baseline mean 15.47 (SD 4.46) F/U 6.94 (SD 4.14) ANOVA analysis mean difference scores of 8.53 C: baseline mean 15.18 (SD 5.46) F/U 11.06 (SD 4.58) ANOVA analysis difference score of 4.12 (F(1, 32)=23.88, p<.0001	NO IMMUNOLOGICAL OUTCOME	Significantly greater improvement on depression scores on the PHQ9 in the intervention	Selection: L Performance : L Detection: L Attrition: H Reporting: L Other: L
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5. Moosa and Jeenah 2012 Soweto, South Africa	Total N= 62 Intervention1 = 19 Intervention 2= 13 Control= 30 M= 15 F= 75 Age= 36.8 (24-53) On ARVs Major depressive disorder assessed according to DSM-IV criteria	Randomised control open label study Intervention 1: Antidepressant (citalopram) 20mg 2/52 Increase by 10-20mg in the absence of improvement Intervention 2: psychotherapy Inter personal therapy (IPT) Delivery and monitoring not specified Controls: not depressed HIV Clinic	Duration of study= 8 weeks 1: Daily dose 2: Number of sessions of IPT= 5-12	Structured Clinical Interview for DSM-IV Axis I Disorders: (SCID-I) and the Hamilton Depression Rating Scale (HAMD)	HAMD mean score I1: Baseline 25.7 (4.5) F/U 6.2 (4) Change: 19.5 I2: baseline 22.5 (4.5) F/U 8.2 (4) Change:14.3 C: Baseline 2.1 (SE 0.30) (95% LCL 1.5; 95% UCL 2.7), with a range from 0 to 5 F/U: 1.62 (SE 0.49) (95% LCL 0.62; 95% UCL 2.62), range from 0 to 14. Difference: 0.6	NO IMMUNOLOGICAL OUTCOME	Improvements in depression outcome in both the IPT and antidepressant arm, with greater improvement observed in antidepressant arm. No comment can be made regarding comparison to control arm, since this is a different population (not depressed)	Selection: H Performance : H Detection: U Attrition: U Reporting: L Other: U
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6. Gaynes et al., 2015 Bamednda, Cameroon	I= 41 M=10 F=31 Age 39.1 (29, 51) On ART (analysis done only participants with 3 months of treatment) Major depression disorder PHQ9> 10 (moderate depressive severity)	Pilot interventional cohort Depression care manager Measurement-Based Care Antidepressant (amitriptyline) prescription, follow up and management of side effects Delivered by non-physician	Sessions = 6 Duration of intervention =3 months	PHQ9 CD4 count Viral load (log) Virologic suppression (< 400 copies/mL) Adherence HIV symptoms decrease Alcohol use Risky sexual behaviour	PHQ9 Baseline score= 14.4 (13.1, 15.6) F/U: 1.6 (0.8, 2.4) Mean difference: - 12.8 (-14, -11.3) Remission (PHQ-9 < 5) = 36 (90%)	CD4 count Baseline 436 (2, 860) F/U: 452 (32, 876) Mean Difference (95% CI): +16 (-47, 79) Viral suppression (% <400 copies/mL) = Baseline: 0 F/U: 5 (18%) Mean Difference (95% CI):18% (4%, 32%)	Improved depression and immunological outcomes. Significance of results not clarified.	Selection: H Performance : L Detection: H Attrition: L Reporting: L Other: L
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7. Abas et al, 2016 Harare, Zimbabwe	N= 9 M= 4 F= 5 Age= 42.1 (35-65) On ART> 4 months Known with adherence problems Probable depression (SRQ8)	Open-label pilot trial Stepped care intervention combining problem-solving therapy for depression with enhanced counselling for antiretroviral therapy adherence ART clinic Delivered by adherence counsellors	Duration of intervention =6 months Number of sessions= 6	Shona Self Report Questionnaire (SRQ-8) CD4 count Viral suppression	SRQ-8 mean baseline= 5.6 F/U: 1.8 Mean difference: 3.8	CD4 count mean baseline= 398.75 mean follow up= 470.86 Mean difference 72,1 Viral load suppression baseline= 57.14 at follow up= 100% Mean difference 42.86%	Improved depression and immunological outcomes. Significance of results not clarified.	Selection: H Performance : H Detection: L Attrition: L Reporting: L Other: L
8. Pence et al., 2014 Bamenda, Cameroon	N = 55 M= 11 F= 44 Age = 40 (33–44) On ART MDD/PHQ9> 10	Interventional trial Measurement-Based Care (MBC) Depression care manager (non-physician) amitriptyline 25–50 mg OD	Duration of intervention = 12 weeks Daily dose Number of sessions= 4	PHQ-9 CD4 count baseline HIV RNA viral load (copies/mL) HIV RNA viral load<400	PHQ-9 Baseline= 13 (12– 16) F/U= 2 (0–3) Change = -11	BASLINE IMMUNOLOGICAL DATA ONLY CD4 baseline = 454 (242–612) Viral load baseline= 12,304 (7,308–21,555)	Significant improvement in depression outcomes: 94 % response to treatment.	Selection: H Performance : H Detection: U Attrition: L Reporting: L Other: L

	(moderate depressive severity)	Delivered by nurse/social – Worker Day hospital AIDS treatment centre						
9. Wagner et al., 2014 Kampala, Uganda	N = 105 M= 19 F= 86 Age= 37 (10) Major depression 80% of participants on ARVs, all medically stable	Interventional longitudinal prospective cohort study Antidepressant: 93% treated with Fluoxetine 20mg OD increasing by 20mg increments 17% treated with imipramine 50 mg increasing to 75mg then 2mg increments Delivery and monitoring not specified HIV clinic	Duration of intervention = 6 months Daily dose	PHQ-9 CD4 count baseline only	PHQ9 mean: Baseline= 16.7(SD 5.2) F/U= 1.9 (SD 3.6) Mean difference= -14.8	BASELINE IMMUNOLOGICAL DATA ONLY CD4 count baseline =346 (SD 243)	Significant improvement in depression outcomes: 86% treatment response	Selection: H Performance : H Detection: H Attrition: L Reporting: L Other: L
10. Ngo et al.,	N= 184	Open label interventional drug trial	Duration of intervention	PHQ-9	PHQ9 mean Baseline: 14.9 (SD	BASELINE IMMUNOLOGICAL	Significant Improved in	Selection: H Performance

2015 Uganda	M=40 F= 144 Age= 36.4 (9.3) 85.9% of participants on ART Major depressive disorder (MINI) Newly started on ART, not on ART, or more than 6 months on ART (mixed group)	fluoxetine (20 mg/day, increments of 20 mg as warranted) or imipramine (50 mg/day, increased to 75mg after two weeks, followed by increments of 25 mg as warranted) Treated by psychiatric medical officers hired and trained by the study HIV/non-HIV clinics	= 6 months Daily dose F/U= 6 months	CD4 count	5.1) F/U: 2.6 (SD 3.8)	DATA ONLY CD4 mean at baseline: 243.6 (SD 214.7)	depression outcomes with 79% treatment response	: H Detection: H Attrition: L Reporting: L Other: L
11. Field and Kruger, 2008 Limpopo, South Africa	Total N= 18 I= 9 C=9 M= 0 F= 18	Non-randomised control trial Art therapy Recruitment: HIV support group Delivery and monitoring not	Duration of intervention = 4 weeks Number of sessions= 1	Beck Depression Inventory II-total out of 63points, >20 depression CHANCE HLOC	BDI-II mean score I= Mean difference= -0.529, SD 0.167 C= -0.1376 SD 0.231 Difference in means:	NO IMMUNOLOGICAL OUTCOME	Significant difference in depression outcomes	Selection: H Performance : L Detection: L Attrition: L Reporting: L Other: H (simultaneous)

	Age= 29.9 (21-42)	specified			-0.39 Significance: (t (16)= 4.11, p<0.05)			s HIV support group sessions)
	ART status not specified							
	BDI> 14 (Mild-mod depression)							
12. Adams et al., 2012 Tanzania	Total N= 20 M= 6 F= 14 Age= ≥18 (not specified further) ARV status not specified Depression at baseline assessed by PHQ-9	Nurse-led antidepressant medication management of depression Amitriptyline (two-week shortage of medication)	Duration of intervention = 12 weeks Daily medication dose 3 follow up visits	PHQ-9 CD4 count baseline only	PHQ9 mean and SD: Baseline= 19.76 (3.01) F/U= 8.12 (1.83) (t = 19.62, df = 16, p < 0.001) Mean difference= 11.64	NO IMMUNOLOGICAL OUTCOME	Significant improvement in depression outcomes	Selection: H Performance : H Detection: H Attrition: L Reporting: L Other: L

13. Andersen et al., 2016 Western Cape, South Africa	N= 14 M= 1 F= 13 Age= 38.4 (7.81) On ART (time not specified) MDD (MINI) psychologist diagnosed	interventional trial Intervention: Nurse-delivered CBT for adherence and depression HIV clinic	Duration of intervention = 2 months Number of sessions= 6-8 F/U= 3 months after completion (5 months after start)	CES-D SDS MINI Hamilton Depression Rating Scale (HAMD)	HAM-D baseline (M = 26.4, SD = 5.5) F/U: (M = 5.8, SD = 5.8), with a very large Effect size (Cohen's d = 2.5) Change : ($\gamma = -0.71$, SE = 0.18, 95% CI [-1.15, -0.28], $t(17) = -3.89$, $p < .01$)	NO IMMUNOLOGICAL OUTCOME	Significant improvement in depression outcomes with a very large effect size	Selection: H Performance : H Detection: H Attrition: U Reporting: L Other: L
14. Olley, 2006 Abuja, Nigeria	N= 62 I= 34 C= 33 M= 27 (43.5%) F= 35 (56.5%) Age= 27.4 (SD 8.1) BDI mean > 14	Non-randomised control trial Intervention: Psycho-education Control: Waitlist Voluntary Counselling and Testing (VCT) centre	Duration of intervention = 4 weeks Number of sessions= 4 x 1 hour, 1 session a weekly	Beck Depression Inventory II-total out of 63points, >20 depression The crown crisp Experiential Index	BDI mean I: Baseline= 19.0 (SD 6.4) F/U= 5.71 (1.5) C: Baseline=17.04 (SD 1.5) F/U= 14.16 (2.5)	NO IMMUNOLOGICAL OUTCOME	Significant improvement in depression outcomes intervention compared to control Main effect F value: 21.06	Selection: H Performance : U Detection: U Attrition: L Reporting: L Other: L

	But not inclusion criteria	Delivered by VCT counsellor	F/U= 4 weeks	Sexual risk behaviour			P<0.00	
	Not on ART, newly diagnosed HIV			Self-disclosure intentions#				
				Coping behaviours				

Appendix 1: PRISMA Flow Diagram

Appendix 2: Search Strategy

Search Terms: Embase, PsychInfo, Medline

1. exp HIV/
2. (HIV or AIDS or (acquired adj2 immunodeficiency adj2 syndrome)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, tc, id, tm, nm, kf, px, rx, ui]
3. exp HIV Infections/
4. exp Human immunodeficiency virus/
5. exp acquired immune deficiency syndrome/
6. OR/1-5
7. exp depression/
8. depress*.mp.
9. exp Depressive Disorder, Major/
10. exp major depression/
11. OR/7-10
12. exp psychoneuroimmunology/
13. psychoneuroimmunology.mp.
14. immunopsychiatry.mp.
15. exp clinical trials/
16. Experiment controls/
17. exp Placebo/
18. exp intervention/
19. exp psychotherapy/
20. (intervention or trial or treatment).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, tc, id, tm, nm, kf, px, rx, ui]
21. control groups/
22. exp "clinical trial (topic)"/
23. exp comparative study/
24. control groups/ or double-blind method/ or single-blind method/
25. exp antidepressant agent/
26. exp intervention studies/
27. OR/12-26
28. (Angola or Benin or Botswana or Burkina Faso or Burundi or Cabo Verde or Cameroon or Central African Republic or Chad or Comoros or Congo, Dem Rep or Congo Rep or Cote d'Ivoire or Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mauritania or Mauritius or Mozambique or Namibia or Niger or Nigeria or Rwanda or (Sao Tome and Principe) or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or South Sudan or Sudan or Swaziland or Tanzania or Togo or Uganda or Zambia or Zimbabwe).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, tc, id, tm, nm, kf, px, rx, ui]
29. exp "Africa south of the Sahara"/
30. Sub-Saharan Africa.mp.
31. remove duplicates from 28-30
32. OR/28-31

6 AND 11 AND 27 AND 32

Appendix 3: Meta-Analysis Formulae

Standardized Mean Gain Depression Outcomes

$$(d) \text{Cohen's } d_{av}: SMG = \frac{(\text{Post intervention mean} - \text{Pre intervention mean})}{\text{Pooled } SD}$$

$$SD_{pooled} = \sqrt{\frac{SD_{baseline}^2 + SD_{final}^2}{2}}$$

$$SE_{gain\ score} = \sqrt{\frac{2(1 - Corr)}{n} + \frac{d_{gain\ score}^2}{2n}}$$

* Corr is the correlation coefficient. No studies included correlation coefficients data, thus a value of 0.5 was assigned as a reasonable and conservative estimate [77].

Unstandardized Mean Gain Immunological Outcomes (where constructs are the same)

Unstandardized mean gain = Post Intervention mean – Pre Intervention mean

Hedge's g

$$Hedge's\ g = Cohen's\ d \times \left(1 - \frac{3}{4N - 9}\right)$$

* N is the total number of participants in the study

Dichotomous Data

$$Odds\ Ratio = \frac{\text{Pre Intervention event (a)}}{\text{Pre intervention no event (b)}} \div \frac{\text{Post Intervention event (c)}}{\text{Post Intervention no event (d)}}$$

$$SE(\ln(OR)) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

Approximation of Dichotomous to Continuous Data

$$Effect\ Size = \ln(OR) \cdot \frac{\sqrt{\pi}}{3}$$

Appendix 4.1 : Effect Size Calculations: Depression Outcomes

Study	Pre Intervention Score Mean	Pre Intervention Score Standard Deviation	Post Intervention Score Mean	Post Intervention Score Standard Deviation	Number of Participants	Standardized Mean Gain (Cohen's d)	Heges g	Standard Error Gain score
Abas, 2015	13.8	2.2	3.1	3.1	14	-4.034	-3.93	0.80
Adams, 2012	19.16	3.01	8.12	1.83	20	-4.81	-4.72	0.77
Andersen, 2016	40.9	8.45	6.58	7.61	14	-4.27	-4.16	0.85
Field & Kruger, 2008					9	-3.17	-3.04	0.82
Gaynes, 2015	14.4	0.825	1.6	0.4	41	-24.98	-24.7	2.70
Hoare, 2014	21.3	5.2	12.3	1	51	-2.90	-2.88	0.28
Ngo, 2015	14.9	5.1	2.6	3.8	184	-2.76	-2.76	0.16
Nyamayaro, 2016	5.6	0.5	1.8	1	9	-5.07	-4.86	1.18
Olley, 2006	19	6.4	5.7	1.5	82	-3.36	-3.35	0.29
Peltzer, 2012	26.8	22.2	19.7	19.3	76	-0.34	-0.34	0.12
Pence, 2014	13	1	2	0.75	55	-12.57	-12.49	1.20
Petersen, 2014	15.47	4.46	6.94	14.4	41	-1.98	-1.97	0.27

Wagner, 2014	16.7	5.2	1.9	3.6	105	-3.36	-3.35	0.25
Moosa, 2012 (pharm)	25.7	4.5	6.2	4	19	-4.59	-4.50	0.78
Moosa, 2012 (IPT)	22.5	4.5	14.3	4	13	-1.93	-1.87	0.47

Appendix 4.2 : Effect Size Calculation: Immune Outcomes, Odds of Viral Suppression

Study	Pre Intervention Odds	Post Intervention Odds	Number of Participants	Log (Odds Ratio)	Standard Error of Change
Abas, 2015	1/13	11/3	14	1.68	1.22
Gaynes, 2015	0/27	5/22	41	1.13	1.50
Nyamayaro, 2016	0/9	5/4	9	1.19	1.55

Appendix 4.3: Effect Size Calculation: Immune Outcomes, CD4 Count (Abas, 2015 result converted from dichotomous viral suppression (VS) to continuous)

Study	Pre Intervention Score Mean	Pre Intervention Score Standard Deviation	Post Intervention Score Mean	Post Intervention Score Standard Deviation	Number of participants	Standardized Mean Gain (Cohen's d)	Hedges g	Standard Error Gain Score
Peltzer, 2012	308	217	384	186	76	0.38	0.38	0.11
Hoare, 2014	454.3	29.5	433.6	214.9	51	-0.17	-0.17	0.14
Gaynes, 2015	436	21405	452	211	41	0.08	0.07	0.16
Nyamayaro, 2016	398.75	157025	470.86	162.5	9	0.46	0.43	0.33
Abas, 2015	VS	VS	VS	VS	14	2.28	2.21	0.27

Highlights

- Pharmacological interventions appeared to have a significantly larger improvement in depression scores than psychological modalities of treatment, in sub-Saharan African studies
- Psychological treatment interventions, incorporating an HIV medication adherence component, had the most pronounced, however non-significant, effect on immune status improvement
- Antidepressant treatment might not be addressing the underlying issues associated with non-adherence in lower-middle income setting of sub-Saharan Africa
- A tentative recommendation from this preliminary evidence is combination treatment for MDD in people living with HIV, using both psychological and pharmacological modalities. However, more evidence of better quality is needed to support future policy in this region.