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Antidepressants for depression in adults with HIV infection.  
*Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD008525.  
DOI: [10.1002/14651858.CD008525.pub3](https://doi.org/10.1002/14651858.CD008525.pub3).

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[Intervention Review]

# Antidepressants for depression in adults with HIV infection

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**Editorial group:** Cochrane Common Mental Disorders Group.

**Publication status and date:** Edited (no change to conclusions), published in Issue 2, 2018.

**Citation:** Eshun-Wilson I, Siegfried N, Akena DH, Stein DJ, Obuku EA, Joska JA. Antidepressants for depression in adults with HIV infection. *Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD008525. DOI: [10.1002/14651858.CD008525.pub3](https://doi.org/10.1002/14651858.CD008525.pub3).

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## ABSTRACT

### Background

Rates of major depression among people living with HIV (PLWH) are substantially higher than those seen in the general population and this may adversely affect antiretroviral treatment outcomes. Several unique clinical and psychosocial factors may contribute to the development and persistence of depression in PLWH. Given these influences, it is unclear if antidepressant therapy is as effective for PLWH as the general population.

### Objectives

To assess the efficacy of antidepressant therapy for treatment of depression in PLWH.

### Search methods

We searched The Cochrane Common Mental Disorders Group's specialised register (CCMD-CTR), the Cochrane Library, PubMed, Embase and ran a cited reference search on the Web of Science for reports of all included studies. We conducted additional searches of the international trial registers including; ClinicalTrials.gov, World Health Organization Trials Portal (ICTRP), and the HIV and AIDS - Clinical trials register. We searched grey literature and reference lists to identify additional studies and contacted authors to obtain missing data. We applied no restrictions on date, language or publication status to the searches, which included studies conducted between 1 January 1980 and 18 April 2017.

### Selection criteria

We included randomized controlled trials of antidepressant drug therapy compared to placebo or another antidepressant drug class. Participants eligible for inclusion had to be aged 18 years and older, from any setting, and have both HIV and depression. Depression was defined according to Diagnostic and Statistical Manual of Mental Disorders or International Statistical Classification of Diseases criteria.

### Data collection and analysis

Two review authors independently applied the inclusion criteria and extracted data. We presented categorical outcomes as risk ratios (RR) with 95% confidence intervals (CIs). Continuous outcomes were presented mean (MD) or standardized mean differences (SMD) with standard deviations (SD). We assessed quality of evidence using the GRADE approach.

## Main results

We included 10 studies with 709 participants in this review. Of the 10 studies, eight were conducted in high income countries (USA and Italy), seven were conducted prior to 2000 and seven had predominantly men. Seven studies assessed antidepressants versus placebo, two compared different antidepressant classes and one had three arms comparing two antidepressant classes with placebo.

Antidepressant therapy may result in a greater improvement in depression compared to placebo. There was a moderate improvement in depression when assessed with the Hamilton Depression Rating Scale (HAM-D) score as a continuous outcome (SMD 0.59, 95% CI 0.21 to 0.96; participants = 357; studies = 6;  $I^2 = 62%$ , low quality evidence). However, there was no evidence of improvement when this was assessed with HAM-D score as a dichotomized outcome (RR 1.10, 95% CI 0.89 to 1.35; participants = 434; studies = 5;  $I^2 = 0%$ , low quality evidence) or Clinical Global Impression of Improvement (CGI-I) score (RR 1.28, 95% CI 0.93 to 1.77; participants = 346; studies = 4;  $I^2 = 29%$ , low quality evidence). There was little to no difference in the proportion of study dropouts between study arms (RR 1.28, 95% CI 0.91 to 1.80; participants = 306; studies = 4;  $I^2 = 0%$ , moderate quality evidence).

The methods of reporting adverse events varied substantially between studies, this resulted in very low quality evidence contributing to a pooled estimate (RR 0.88, 95% CI 0.64 to 1.21; participants = 167; studies = 2;  $I^2 = 34%$ ; very low quality evidence). Based on this, we were unable to determine if there was a difference in the proportion of participants experiencing adverse events in the antidepressant versus placebo arms. However, sexual dysfunction was reported commonly in people receiving selective serotonin reuptake inhibitors (SSRIs). People receiving tricyclic antidepressants (TCAs) frequently reported anticholinergic adverse effects such as dry mouth and constipation. There were no reported grade 3 or 4 adverse events in any study group.

There was no evidence of a difference in follow-up CD4 count at study termination (MD -6.31 cells/mm<sup>3</sup>, 95% CI -72.76 to 60.14; participants = 176; studies = 3;  $I^2 = 0%$ ; low quality evidence). Only one study evaluated quality of life score (MD 3.60, 95% CI -0.38 to 7.58; participants = 87; studies = 1; very low quality evidence), due to the poor quality evidence we could not draw conclusions for this outcome.

There were few studies comparing different antidepressant classes. We are uncertain if SSRIs differ from TCAs with regard to improvement in depression as evaluated by HAM-D score (MD -3.20, 95% CI -10.87 to 4.47; participants = 14; studies = 1; very low quality evidence). There was some evidence that mirtazapine resulted in a greater improvement in depression compared to an SSRI (MD 9.00, 95% CI 3.61 to 14.39; participants = 70; studies = 1; low quality evidence); however, this finding was not consistent for all measures of improvement in depression for this comparison.

No studies reported on virological suppression or any other HIV specific outcomes.

The studies included in this review had an overall unclear or high risk of bias due to under-reporting of study methods, high risk of attrition bias and inadequate sequence generation methods. Heterogeneity between studies and the limited number of participants, and events lead to downgrading of the quality of the evidence for several outcomes.

## Authors' conclusions

This review demonstrates that antidepressant therapy may be more beneficial than placebo for the treatment of depression in PLWH. The low quality of the evidence contributing to this assessment and the lack of studies representing PLWH from generalized epidemics in low-to middle-income countries make the relevance of these findings in today's context limited. Future studies that evaluate the effectiveness of antidepressant therapy should be designed and conducted rigorously. Such studies should incorporate evaluation of stepped care models and health system strengthening interventions in the study design. In addition, outcomes related to HIV care and antiretroviral therapy should be reported.

## PLAIN LANGUAGE SUMMARY

### Antidepressant drugs for treatment of depression in people living with HIV

#### Why is this review important?

Depression is very common among people living with HIV. There are many unique issues which influence the development and possibly the recovery from depression in this group. We are therefore uncertain whether the antidepressant drugs which are usually used to treat depression in people without HIV will be as effective in PLWH.

#### Who will be interested in this review?

PLWH, general practitioners, HIV clinicians and professionals working in mental health services.

#### What questions does this review aim to answer?

- Are antidepressant medicines more effective than using a placebo (pretend treatment) for treatment of depression in PLWH?
- Do more people stop attending services (dropout) if they are receiving antidepressant medicines compared to placebos?

- Are there any serious side effects to antidepressant medicines which specifically affect PLWH?
- Which type of antidepressant medicine is most effective for depressed PLWH?
- Does treating depression with antidepressants in PLWH improve antiretroviral treatment outcomes among people also receiving HIV treatment?

**Which studies were included in the review?**

We searched several databases to find randomized controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) which compared antidepressant therapy to placebo or other antidepressant drugs for treatment of depression in PLWH. Studies had to have been conducted between 1 January 1980 and 18 April 2017 to be included in the review. Ten studies with 709 participants were included.

**What does the evidence from the review tell us?**

Most studies were conducted more than a decade ago, in the USA, in predominantly men. We found that antidepressant therapy may improve depressive symptoms when compared to a placebo tablet. There was no clear evidence of a difference in the number of people who dropped out of care when comparing people who received antidepressants with people who received a placebo. We cannot be certain if one type of antidepressant works better than another. Side effects were very common among all study participants. Although there were no clear conclusions on which side effects were most common or if side effects occurred more frequently in people taking antidepressants compared to a placebo, participants receiving antidepressants called selective serotonin reuptake inhibitors did report sexual problems frequently. People receiving medicines called tricyclic antidepressants reported constipation and dry mouth frequently. No studies reported on how antidepressant therapy affected the effectiveness of antiretroviral therapy. The evidence used to generate several of the results was assessed as low or very low quality.

**What should happen next?**

The review authors recommend that new studies on treatment of depression should be conducted in countries and population groups where HIV is most common. These studies should evaluate what causes depression in these populations and how to best to incorporate antidepressant therapy with other strategies for the management of PLWH and depression.