Published in final edited form as:
Ann Behav Med. 2014 June ; 47(3): 259–269. doi:10.1007/s12160-013-9559-6.

Depression Treatment Enhances Adherence to Antiretroviral Therapy: A Meta-Analysis

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Abstract

BACKGROUND—Depression is a risk factor for nonadherence to HIV/AIDS treatment.

PURPOSE—A meta-analysis was conducted to examine whether treatment of depression and psychological distress improves antiretroviral therapy adherence.

METHODS—PubMed and PsycINFO databases were systematically searched for relevant articles. Studies that reported an association between depression treatment (or an intervention with a component addressing mental health) and antiretroviral adherence were included.

RESULTS—Across 29 studies of 12,243 persons living with HIV/AIDS, treatment of depression and psychological distress improved antiretroviral adherence ($p < .001$). The odds of a person adhering were 83% better if he/she was treated for depression. Greater improvements in adherence were found for samples with lower CD4 counts or more severe depression, for interventions specifically targeting depression (versus addressing mental health as a secondary objective), longer treatments, and observational studies.

CONCLUSIONS—These findings support the need for detection and treatment of depression among persons living with HIV/AIDS.

Keywords

depression; HIV/AIDS; adherence; compliance; antiretroviral therapy; meta-analysis

Introduction

Individuals living with HIV/AIDS are at increased risk for psychiatric disorders. In a nationally representative sample of U.S. outpatient HIV patients, nearly half screened positive for at least one psychiatric disorder, including major depression, dysthymia, generalized anxiety, and panic disorder (1). HIV-positive individuals are at a twofold (2) to fivefold (1) greater risk for depression than are HIV-negative individuals.

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Conflict of Interest Statement: The authors have no conflict of interest to disclose.

Depressive symptoms are associated with relatively worse health outcomes in HIV patients (3–7), partly due to the mediating role of nonadherence to antiretroviral therapy (ART). Depression is linked to nonadherence in many chronic medical conditions (8, 9); the odds of medical treatment nonadherence are three times greater among depressed patients compared to nondepressed patients (8). A recent meta-analysis across 95 samples found depressive symptoms were significantly related to ART nonadherence (10). Furthermore, longitudinal data suggest that reductions in depression over time are associated with improvements in ART adherence (11).

Adherence is critical for optimal health outcomes, including sustained viral load suppression, increased CD4 lymphocyte count, and decreased risk of opportunistic infection or death (12–15). Near-perfect adherence of over 95% is associated with better virologic outcomes (15) and lower risk of mortality (16). Yet, only 62% of HIV-infected persons worldwide report greater than 90% adherence to highly active ART (HAART) (17). In North America, an estimated 55% of HIV-infected individuals achieve adequate levels of adherence to ART (18).

Given the cross-sectional and longitudinal data linking depression and ART nonadherence, depression treatments offer a promising strategy for improving adherence. Some observational studies suggest that depression treatment is associated with better ART adherence. AIDS-infected individuals are 30% more adherent to HAART in a given month if they used antidepressants in the prior month (19). Initiation of depression treatment is associated with better ART adherence in persons living with HIV/AIDS (20). In addition, among HIV-infected individuals with depression, those who adhere to their antidepressant treatment demonstrate greater ART adherence (20, 21). However, randomized controlled trials that aim to improve mental health—although effective for relieving depressive symptoms—have offered mixed results for improvement in ART adherence (22, 23).

The present study is a quantitative review of the literature with meta-analysis to assess the degree to which the treatment of depression in HIV/AIDS patients is effective for improving ART adherence. Meta-analytic techniques also permit the examination of moderating factors to determine which factors may be associated with better adherence outcomes after treatment. Depression treatments for persons with HIV/AIDS—and mental health interventions more generally—vary considerably in methodology (such as study design, type of control group, sample size, and adherence measurement), depression treatment characteristics (e.g., treatment duration, individual vs. group delivery of psychotherapy), and sample characteristics (e.g., gender composition, median viral load and CD4 count). These moderating factors are examined here.

Methods

Literature search and inclusion/exclusion criteria

A comprehensive literature search was conducted using the PubMed and PsycINFO databases for relevant English-language studies published through November 2012. The following combinations of keywords were used: *adherence* (or adher*, nonadher*, non-adher*, complian*, noncomplian*, or non-complian*, or persistence) and *HIV* (or AIDS,

antiretroviral, HAART, human immu* virus, or acquired immu* syndrome) and *depression* (or depress*, distress, mental health, or mental illness).

For this meta-analysis, adherence to ART was defined as following ART recommendations as prescribed by a health care provider. Studies included in this meta-analysis had variable definitions of adherence; the definition and assessment of adherence within each individual study was maintained. For example, some studies considered a person adherent if he or she followed the prescribed treatment 100% of the time (24–26); other studies defined adherence as following the prescribed treatment 95% of the time (21, 23) or 90% of the time (20, 27, 28), and others analyzed adherence as a continuous variable (22, 29, 30).

Depression treatment was broadly defined as any intervention with a component aimed at alleviating depressive symptoms or psychological distress, or at improving mental health. Treatments that focused on relieving depression (e.g., psychotherapy, antidepressant medication), anxiety, or stress (e.g., mindfulness-based stress reduction, cognitive behavioral stress management) were included. In addition, interventions were included if they were not primarily focused on relieving psychological distress—including adherence interventions, peer support, and side effects coping skills interventions—but did contain a module or component addressing the management of negative thoughts or emotions, coping with stress, or improving mental health.

Studies were included in the meta-analysis if they provided an effect size relating depression treatment or mental health intervention to ART adherence (or data to calculate an effect size). Literature reviews or interventions that did not address mental health were excluded. Although substance abuse and psychotic disorders often co-occur with depression in persons living with HIV/AIDS, these conditions were beyond the scope of this meta-analysis; thus, treatments for substance abuse and psychotic disorders were excluded.

Data extraction and effect size calculation

For each study, the reference, the measure of depression or mental health, and the definition of adherence were recorded. The following data were coded for moderator analyses: (a) *percent of sample that is female*; (b) *median or mean HIV-1 viral load* (copies/mL), or percent of sample with undetectable viral load; (c) *mean or median CD4 count* (cells/μL); (d) *severity of depression* among study participants (i.e., clinical diagnosis of depression, severity based on reported scores, or no inclusion criteria regarding depression severity); (e) *treatment objective* (depression treatment vs. other intervention with a mental health component); (f) *integration of depression treatment with adherence training* vs. no adherence training; (g) *intervention duration* in number of sessions or weeks; (h) *psychotherapy format* (delivered individually vs. in a group); (i) *study design* (observational, non-randomized controlled trial, or randomized controlled trial [RCT]); (j) *comparison group* (standard care or wait-list control vs. “active” control group, such as a psychoeducational program); (k) *sample size*; and, (l) *adherence measure* (self-report vs. pharmacy refill record or electronic pill cap monitoring).

The effect size, representing the impact of the depression treatment or mental health intervention on ART adherence at post-intervention, was extracted for each study. (For

observational studies, the effect size indicated a non-causal relationship between depression treatment and ART adherence.) We also recorded the effect of depression treatment on subsequent depressive symptoms, as well as the association between improvements in depressive symptoms and improvements in ART adherence. The effect size *r* was used because it represents both the magnitude and direction of the effect; a positive *r* here indicates that the depression treatment *increased* adherence to ART, and a negative effect size indicates that the treatment *decreased* adherence. When the effect size *r* was not provided in the journal article, data from Cohen's *d*, *F*, *t*, χ^2, group means and standard deviations, or exact *p* values were used to calculate *r* (31). Odds ratios were converted to Cohen's *d* using the approach described by Chinn (32); Cohen's *d* was then converted to *r* (31). When results were simply reported as "significant" but exact *p* values were not provided, the one-tailed *p*-value was assumed to be .05 (33). When results were described as "nonsignificant" without exact *p* values given, the one-tailed *p* was assumed to be .50 and *r* was assumed to be 0. In cases in which there were multiple effects from an individual study (such as several measures of adherence correlated with receipt of depression treatment), the effect sizes were converted to Fisher's *Z* transformation of *r* (Z_r) and averaged to obtain one overall effect size (a conservative approach) (33). For studies with multiple follow-up assessments, the effect size for the assessment immediately post-intervention was used; follow-up data were excluded from analyses because of the heterogeneity in follow-up periods across studies. Please refer to the Electronic Supplementary Material for coded information and effect sizes for all studies included in this meta-analysis.

Statistical analyses

Meta-analytic tests were conducted using both fixed effects and random effects models. The fixed effects approach is statistically powerful and appropriate for small-size meta-analyses, although the results are limited in generalizability to the sample of studies included in the meta-analysis. The random effects approach, on the other hand, is more stringent but the findings allow generalization to other similar studies outside this sample (34).

Significance tests—Significance tests were conducted to determine the probability that the mean effect size of this sample is significantly different from zero. For the fixed effects approach, one-tailed *p*-values were converted to *Z* scores and combined using the Stouffer method (35). For the random effects approach, a one-sample *t*-test was conducted on the Fisher-transformed *r* effect sizes.

Fail-safe *N*—Studies that show positive results (i.e., depression treatment is effective for improving ART adherence) may be more likely to be published than those that show null or negative results. To address this possible publication bias, the fail-safe *N* was computed to obtain the number of new, unpublished, or unretrieved studies averaging null results that must exist to render the overall findings nonsignificant (36). The tolerance for null results was computed to estimate the number of unretrieved studies that are likely to exist, based on the conservative assumption that there may be five unpublished studies for every one published study (31).

Tests of heterogeneity—Heterogeneity between studies was evaluated using Cochran's Q and I^2. Cochran's Q is a significance test (distributed as chi-squared), indicating whether the set of effect sizes is heterogeneous (37, 38). I^2 is the proportion of total variance across studies due to heterogeneity rather than chance. Low, moderate, and high I^2 values are roughly estimated to be 25%, 50%, and 75%, respectively (39). If the effect sizes are found to be heterogeneous, then moderator analyses should be conducted to account for the variability.

Moderator analyses—Linear contrast weights (λ) representing our predictions were used to conduct contrast tests based on the fixed effects model (33). For the random effects approach, correlations were computed between the Fisher-transformed *r* effect sizes and their corresponding contrast weights for categorical variables. Continuous variables (such as the percent of females in each study sample) were analyzed within the random effects framework by correlating the Fisher-transformed *r* effect sizes with the values of the moderator variable.

Results

Depression treatment and ART adherence

The literature search yielded 29 studies, published between 2001 and 2012, that met the inclusion criteria (see Figure 1 for the study flow diagram). Table 1 lists the types of interventions included in the meta-analysis and provides references. The studies encompassed a total of 12,243 persons with HIV/AIDS, with a median sample size of 156 participants per study. The *r* effect sizes, representing the association between depression treatment and ART adherence, ranged from −.25 to .80. Twenty-one studies (72%) had effect sizes in the positive, predicted direction, reflecting a positive influence of depression treatment on ART adherence. Four studies (14%) showed null results, and four studies (14%) had effect sizes in the negative, unpredicted direction.

The unweighted mean *r* of .15 (95% confidence interval [CI] = .06, .23) was highly significant based on both the fixed effects ($Z = 11.44$, one-tailed $p < .001$) and random effects ($t_{(28)} = 3.39$, one-tailed $p = .001$) tests, indicating that depression treatments were associated with improved ART adherence (Table 2). Nonadherence was 35% greater among HIV/AIDS-infected persons who did not receive depression treatment (standardized relative risk = 1.35; 95% CI = 1.13, 1.60), and the odds of a person adhering were 83% better if he or she was treated for depression or psychological distress (standardized odds ratio [OR] = 1.83; 95% CI = 1.27, 2.55). The fail-safe *N* indicated that 1373 unpublished or unretrieved studies averaging null results must exist to render these findings nonsignificant; this number exceeded the tolerance level of 155 "file drawer" studies that possibly exist (36). Moreover, the set of effect sizes was heterogeneous (Cochran's Q: $\chi^2_{(28)} = 92.67$, one-tailed $p < .001$), suggesting that moderator variables may account for the heterogeneity. Nearly 70% of the total variance across studies was due to heterogeneity rather than chance ($I^2 = 69.79\%$).

Moderators of the association between depression treatment and ART adherence

Participant characteristics—As shown in Table 3, the proportion of the sample that was female was not related to the effect size, based on the random effects analysis ($r = -.20$, one-tailed $p = .16$). Depression treatments were more effective for improving adherence in studies where individuals had, on average, CD4 cell counts that were below the median of 421 cells/μL, according to the fixed effects model ($Z = 3.78$, $p < .001$; near-significant trend for the random effects analysis: $r = .39$, $p = .07$). The reporting of HIV-1 viral load varied across studies; for example, some studies reported mean or median viral load, others reported the proportion of the sample with viral load below a particular level, and others reported the proportion of the sample with undetectable viral load. We were unable to categorize studies based on HIV-1 viral load and therefore did not test viral load as a moderator.

To examine depression severity as a moderating variable, studies were coded based on whether a clinical diagnosis of depression was required for entry in the study. Furthermore, among the studies that did not require participants to have clinical depression, some reported the average depression severity in the samples using established scales with validated cut-points (including the Beck Depression Inventory and the Center for Epidemiologic Studies Depression Scale). We categorized studies into one of two groups: (a) studies in which all participants had a clinical diagnosis or the average level of depressive symptoms was moderate-to-severe, and (b) studies that had no inclusion criteria for depression, and the average severity was unreported or mild. The 15 studies in which participants with clinical depression or moderate-to-severe symptoms found a stronger effect of depression treatment on ART adherence, compared to the 14 studies in which participants had milder depressive symptoms (fixed effects: $Z = 3.72$, $p < .001$; random effects: $r = .30$, $p = .055$).

Depression treatment moderators—Many of the studies contained elements that were combined with depression treatment, such as adherence training, peer support, and development of coping skills. To more accurately examine the association between depression treatment and ART adherence, two moderators were tested: the treatment or intervention objective, and whether the intervention was integrated with adherence training. First, treatments that had the primary goal of relieving depression (i.e., cognitive behavioral therapy or antidepressant treatment), rather than addressing mental health as a secondary matter (i.e., adherence, peer support, or psychoeducational interventions), were more effective for improving ART adherence (fixed effects: $Z = 5.20$, $p < .001$; random effects: $r = .43$, $p = .01$). Next, among the trials only (i.e., excluding observational studies), the 10 mental health interventions that were integrated with adherence training had, overall, the same impact on ART adherence as the 7 trials without adherence training (fixed effects: $Z = 0.01$, $p = .50$; random effects: $r = .001$, $p = .50$).

Depression treatments were categorized based on whether they spanned up to 8 sessions or weeks, 9 to 16 sessions or weeks, or at least 17 sessions or weeks. A significant linear trend emerged, in which depression treatments that were longer in duration resulted in greater adherence rates than shorter treatments, based on both the fixed effects ($Z = 4.76$, $p < .001$) and random effects models ($r = .43$, $p = .02$).

Among 15 studies of psychotherapy and psychosocial interventions, individual psychotherapy was more effective for enhancing ART adherence than group psychotherapy or group interventions (fixed effects model: $Z = 2.67$, $p = .004$). The more generalizable random effects model only approached significance ($r = .41$, $p = .07$).

Methodological moderators—Observational studies—in which depression treatment was used to predict ART adherence—had larger effect sizes than did RCTs, based on both fixed effects ($Z = 2.99$, $p = .001$) and random effects models ($r = .33$, $p = .04$). (Two non-randomized controlled trials were excluded from the moderator analysis because there were not enough to create a separate group). Interventions that employed a standard care or wait-list control group were no more effective than interventions with "active" control conditions (e.g., receiving psychoeducational materials) (fixed effects: $Z = 0.03$, $p = .49$; random effects: $r = .002$, $p = .50$). Studies with sample sizes above the median (of more than 156 participants) had results similar to those with sample sizes below the median (fixed effects: $Z = -.38$, $p = .35$; random effects: $r = -.03$, $p = .44$). Finally, studies that measured adherence using objective methods (i.e., electronic pill cap monitoring or pharmacy refill records) found a greater association between depression treatment and ART adherence, compared to studies that assessed adherence with self-report scales, according to the fixed effects analysis ($Z = -2.65$, $p = .004$) but not the random effects analysis ($r = -.19$, $p = .16$).

Are these interventions effective for alleviating depressive symptoms?

As a secondary analysis, we meta-analyzed the overall effect of depression treatments and mental health interventions on subsequent depressive symptoms within this sample of studies. Of the 17 intervention studies (15 RCTs and 2 non-randomized controlled trials), 11 RCTs reported depressive symptoms as an outcome. Eight of the 11 interventions showed results in the predicted direction, whereas three studies found no effect of the intervention on depressive symptoms.

Across 1,293 participants in these 11 studies, the mean r effect size of 0.18 (95% CI = .08, .29) demonstrated that the interventions were effective for improving depressive symptoms (fixed effects: $Z = 5.68$, one-tailed $p < .0001$; random effects: $t_{(10)} = 3.74$, one-tailed $p = .002$; Table 2). The odds of experiencing an improvement in depressive symptoms were twice as high among participants in the intervention groups, compared to those in the control groups (standardized OR = 2.07; 95% CI = 1.38, 3.30). There was a statistically significant and moderately large degree of heterogeneity across studies ($Q = 24.68$, $p = .01$; $I^2 = 59.48\%$).

The fail-safe N indicated that 120 unpublished or unretrieved studies averaging null results must exist to render these findings nonsignificant. However, because we did not conduct a systematic literature search regarding the effect of depression treatment on depressive symptoms among persons with HIV/AIDS, these results may not be representative of all published studies on this topic.

Are improvements in depressive symptoms associated with improvements in ART adherence?

Of the 29 studies in the meta-analysis, only one study formally tested change in depressive symptoms or psychological distress as a predictor of change in ART adherence; the study found no significant relationship between the rate of change in psychological distress and change in adherence (40). Studies of collaborative care for depression (23) and cognitive behavioral stress management (22, 41) did show improvements in depression outcomes but not ART adherence. However, cognitive behavioral interventions targeting depression and/or ART adherence found positive effects for both outcomes (30, 42) or for related psychosocial outcomes, such as coping skills (25) and perceptions of improvement in one's mental health (43). Furthermore, six studies reported that adherence to depression treatment (such as adherence to antidepressant therapy or the number of psychotherapy sessions attended) was associated with adherence to ART (20, 21, 27, 29, 44, 45).

Discussion

Depressive symptoms are known to increase risk for poor adherence to antiretroviral therapy. Evidence regarding the effect of depression treatment on ART adherence has been inconclusive. This meta-analysis investigated whether, and to what extent, the treatment of depression and psychological distress is associated with improvements in ART adherence. Data from 29 studies—encompassing a total of 12,243 persons living with HIV/AIDS—were synthesized and revealed that depression treatments and mental health interventions are, in fact, effective for enhancing adherence to antiretroviral regimens. The odds of a person adhering to ART are 83% better if he or she is treated for depression, and the risk of nonadherence is 35% greater among those who do not receive depression treatment. As expected, these interventions were also effective for improving depressive symptoms.

The average effect size representing the association between depression treatment and ART adherence (r = .15) appears numerically modest, yet it is highly significant based on both the fixed effects model and the stringent random effects model. In the context of medical interventions, even very small effect sizes can have a substantial impact when considered on a large scale (33, 46). Given the high prevalence of depression among persons living with HIV (1) and the robust association between depressive symptoms and ART nonadherence (10), the potential health benefits of depression treatment should not be understated.

Furthermore, this meta-analysis found moderating factors that accounted for some of the variability in effect sizes across studies. First, studies with participants who had, on average, lower CD4 cell counts showed relatively stronger effects of depression treatment on ART adherence. Similarly, studies in which participants were diagnosed with clinical depression or had, on average, moderate-to-severe depressive symptoms demonstrated larger effects than studies in which participants had mild depressive symptoms or were not required to have clinical depression for study entry. It is possible that individuals with lower CD4 counts or more severe depression may have more room for improvement in terms of increasing ART adherence and enhancing mental health. Indeed, previous work has shown that—among patients with serious illnesses (including HIV/AIDS, cancer, and cardiovascular disease)—those who were in worse health tended to be less adherent,

compared to those in better health (47). Patients who are severely ill may be more likely to encounter physical, psychological, and practical limitations that hinder their efforts at adherence and thus may garner more benefits from depression treatment than their healthier counterparts. However, the moderator results regarding CD4 count should be interpreted with caution due to the small number of studies and the high variability in effect sizes across studies.

Next, this meta-analysis uncovered several aspects of interventions that were associated with greater gains in adherence. Interventions or treatments that are longer in duration tend to be more effective for enhancing adherence. The persistent cognitive, motivational, behavioral, and social deficits associated with depression are likely to require sufficient time and substantial effort to be fully addressed. Antidepressant treatments, for example, require weeks for clinical improvement to become evident, and patients often need dosage adjustments, augmentation, or switching of medications. In addition, psychotherapies or counseling delivered one-on-one may be more effective for enhancing ART adherence than those delivered in a group setting. Individually-delivered psychotherapy or counseling has the advantage of being tailored specifically to the client's needs; however, this moderator finding may not be generalizable to studies outside of the meta-analysis because it was only marginally significant according to the random effects model.

This meta-analysis consisted of a wide range of studies that included not only standard depression treatments, but also relevant interventions that addressed mental health or psychological stress. Moderator analyses were used in an attempt to "isolate" the effect of depression treatment on ART adherence. Interventions or treatments with the primary goal of alleviating depression (including antidepressant treatment or psychotherapy) were more strongly associated with improvements in ART adherence than were interventions that address mental health as a secondary matter (such as behavioral or other psychosocial interventions). Also, to address the confounding effect of adherence training, we compared mental health interventions that were integrated with adherence training to those without adherence training. Although adherence training did not appear to provide additional benefits for ART adherence, this null result may be due to the small sample of RCTs and the high variability. Previous meta-analyses have found that behavioral, psychosocial, and adherence interventions are effective for improving ART adherence, although the effects are overall modest and heterogeneous (48, 49). Efforts to improve adherence are likely to require an intensive, multifaceted approach; our findings suggest that depressive symptoms, if present, should not be overlooked. Indeed, RCTs of cognitive behavioral therapy that target both depression and adherence have shown promising results (30, 42).

Among the methodological moderators tested, study design explained some of the variation in effect sizes. In particular, observational studies showed a much stronger association between depression treatment and ART adherence than did RCTs. The observational studies lacked the rigorous control of RCTs and may have failed to adjust for some confounding factors. An alternative explanation is that the RCTs were highly variable (some interventions were more effective than others), whereas the observational studies were homogeneous and primarily focused on antidepressant treatment. Lastly, a small sample of studies employing objective measures of adherence (electronic pill cap monitoring or pharmacy refill data)

produced a stronger relationship between depression treatment and ART adherence than studies that relied on self-report. Other meta-analyses of ART adherence have found similar results (10, 48).

Limitations

Several limitations should be considered when interpreting the results of this meta-analysis. First, causal conclusions cannot be drawn regarding the effect of depression treatment on ART adherence. The observational studies included in this meta-analysis provide strong support for a *relationship* between being treated for depression and subsequently improving adherence to ART. Confounding variables could be responsible for both engaging in depression treatment and improving ART adherence in the observational studies. Although there was not enough evidence to conclude that improvements in depressive symptoms were linked to improvements in adherence, multiple studies in the meta-analysis reported that adherence to depression treatment predicted adherence to ART (20, 21, 27, 29, 44, 45). Future interventions should examine whether the alleviation of depression mediates changes in ART adherence.

Second, readers should be careful in drawing conclusions based on the moderator results. These analyses required studies to be stratified into subgroups; some of the subgroups were small and highly variable (i.e., with confidence intervals crossing zero). Although the mean effect size for some subgroups made it appear as if these interventions were not effective for improving adherence, these subgroups may have been underpowered. In addition, meta-analytic techniques only permit the examination of moderators between studies, but not within studies. More work is needed to test the moderators found in this meta-analysis. For example, it is important to evaluate whether depression treatment produces relatively greater gains in adherence among persons with more severe depressive symptoms.

Third, the types of mental health interventions and depression treatments included in this meta-analysis varied widely. Antidepressant treatment was the only treatment or intervention with a sizable number of studies. The other interventions contained components addressing mental health or psychological distress (e.g., identifying and restructuring irrational thoughts, managing stress and negative emotions, and cultivating social support); these other components were confounded with depression treatment. However, the diversity of interventions could be perceived as a strength of this meta-analysis because it increases the generalizability of the findings. That is, the alleviation of depressive symptoms and the promotion of mental health—using a variety of strategies—is associated with improvements in ART adherence.

Finally, this meta-analysis may have been limited by incomplete retrieval of relevant studies and reporting bias. Research databases were systematically searched, and the search results were carefully reviewed based on the inclusion and exclusion criteria. Nonetheless, we may have inadvertently missed relevant studies. The findings from the literature may also be skewed due to the “file drawer problem,” which reflects the higher likelihood for significant results to be published, compared to null results. However, the fail-safe *N* suggests that 1373 studies averaging null results must exist to render the meta-analytic findings nonsignificant. Therefore, we are reasonably confident that these findings are resistant to publication bias.

Implications for future research

The findings of this meta-analysis raise questions that should be addressed in future research studies. First, more research is needed to compare the effectiveness of different depression treatments for improving ART adherence. Although evidence strongly supports the benefits of antidepressant treatment, less is known regarding the effects of psychotherapy—such as cognitive behavioral therapy or interpersonal therapy—on ART adherence. There is also individual variation in preferences for and responses to depression treatments, such that personal characteristics (e.g., cultural values, depression severity) and comorbidities (including substance use) are important for determining which form of treatment is most appropriate and beneficial for a particular person.

Next, the specific pathways whereby depressive symptoms lead to poor adherence are not well-understood. The relationship between depressive symptoms and ART nonadherence may be mediated by a number of factors, such as low motivation, poor memory, hopelessness, and the lack of social support. Recent work suggests that the cognitive symptoms of depression—including depressed mood, loss of interest, hopelessness, poor concentration, worthlessness, and guilt—may be more predictive of ART nonadherence than are vegetative symptoms (i.e., disturbances in appetite and sleep, agitation) (11). The exact mechanisms responsible for the link between depression and nonadherence must be identified to effectively tailor interventions and to maximize the benefits of depression treatment.

Furthermore, little is known regarding the long-term effects of depression treatment on ART adherence. This meta-analysis synthesized data from assessments made immediately post-intervention because studies varied in the duration of their follow-up periods. If depressive symptoms are, in fact, responsible for ART nonadherence, then we would expect the adherence-related benefits of depression treatment to last as long as depressive symptoms are well-managed. In practice, individuals with a history of depression should be monitored for the possible recurrence of depressive symptoms.

Finally, depression is likely to have both direct and indirect effects on morbidity and mortality in HIV/AIDS (50). This meta-analysis examines only one possible mediator, nonadherence to ART. More work is needed to determine whether and how depression treatment may produce improvements in disease markers. Psychological interventions have been shown to improve neuroendocrine regulation and immune status in persons with HIV (51), suggesting that depression treatment may lead to improvements in both mental and physical health.

Conclusions

A wealth of empirical evidence has demonstrated a robust link between depression and nonadherence to antiretroviral therapy. In this meta-analysis of 29 studies, we found that the treatment of depressive symptoms and alleviation of psychological distress are associated with improvements in adherence to antiretroviral therapy. Efforts to improve adherence should consider the detrimental effects of untreated depression. In light of the scope of depression and suboptimal adherence to antiretroviral therapy among persons living with

HIV/AIDS, these findings suggest that the effective management of depression may result in considerable improvements in health outcomes and quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Nancy Sin was supported by Institutional Training Grant 5T32AG000212-20 from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding source. Sin is now affiliated with The Pennsylvania State University. We thank Bob Rosenthal for his statistical advice.

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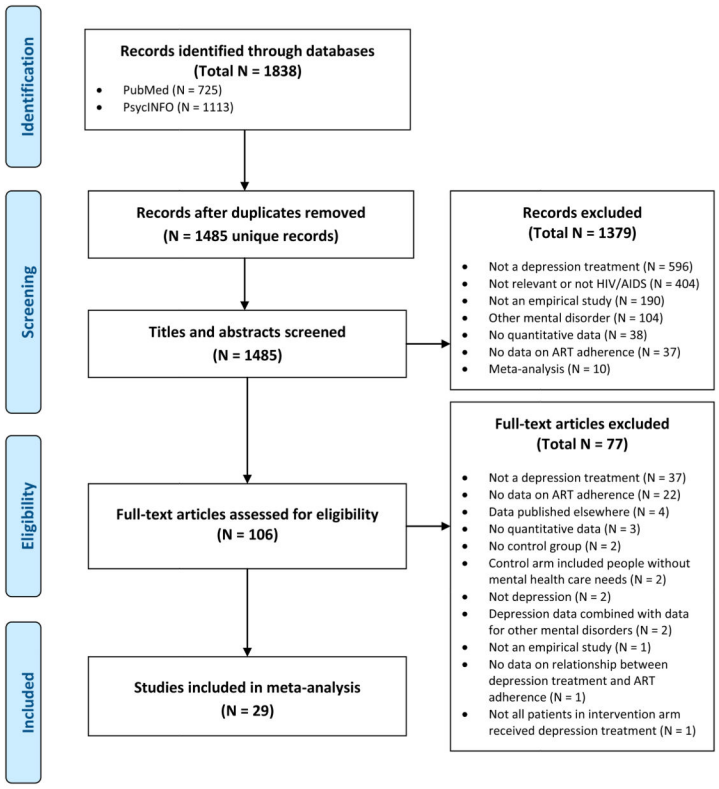

Figure 1.
Study flow diagram

Table 1

Types of Depression Treatments and Mental Health Interventions Included in the Meta-Analysis

Treatment Type	No. of Studies	References
Treatments in which alleviation of depression is the primary objective		
Antidepressant	10	(19, 21, 27, 29, 44, 45, 52–55)
Cognitive behavioral therapy	2	(30, 42)
Antidepressant or psychotherapy/psychiatric care	2	(20, 56)
Collaborative care for depression	2	(23, 57)
Interventions that include a component on relieving psychological distress or enhancing mental health		
Cognitive-behavioral intervention for stress management	2	(22, 41)
Cognitive-behavioral interventions for health behaviors (e.g., adherence, risky sexual behaviors)	2	(43, 58)
Other interventions for preventive health behaviors or coping with side effects	2	(25, 28)
Mindfulness-based stress reduction	1	(24)
Psychosocial interventions (e.g., support groups, peer support)	6	(26, 40, 59–62)

Table 2

Summary of Meta-Analysis Findings for the Associations of Depression Treatment with Antiretroviral Adherence and Subsequent Depressive Symptoms

	Outcome	
Meta-Analytic Results	**Antiretroviral Adherence**	**Depressive Symptoms**
Study Characteristics		
No. of Studies	29	11
Total *N*	12,243	1,293
Median *N* per study	156	89
Unweighted r effect size		
Mean *r* (95% CI) [a]	.15 (.06, .23)	.18 (.08, .29)
Median *r*	.13	.21
Min, Max	−.25, .80	.00, .39
SD	.19	.16
Significance tests[b]		
Fixed effects analysis	$Z = 11.44$, $p < .001$	$Z = 5.68$, $p < .001$
Random effects analysis	$t(28) = 3.39$, $p = .001$	$t(10) = 3.74$, $p = 0.002$
Fail-Safe N (Tolerance)[c]	1373 (155)	120 (65)
Standardized Odds Ratio (95% CI)[d]	1.83 (1.27, 2.55)	2.07 (1.38, 3.30)
Standardized Relative Risk (95% CI) [d]	1.35 (1.13, 1.60)	1.44 (1.17, 1.82)
Heterogeneity		
Cochran's Q (χ^2 test)	$\chi^2(28) = 92.67$, $p < .001$	$\chi^2(10) = 24.68$, $p = .01$
I^2	69.79%	59.48%

[a] Confidence intervals were computed based on the stringent random effects model.

[b] All *p* values are one-tailed, reflecting the hypothesis that depression treatment is associated with improved antiretroviral adherence.

[c] The fail-safe *N* is the number of new, unpublished, or unretrieved ("file drawer") studies averaging null results that would need to exist to render these findings nonsignificant. The tolerance for null results is a conservative estimate of the number of file drawer studies that possibly exist.

[d] Standardized relative risk, standardized odds ratio, and their confidence intervals were calculated from the mean *r* effect size using the binomial effect size display (31).

Table 3

Summary of Moderator Findings for the Association Between Depression Treatment and Antiretroviral Adherence

Moderator	No. of studies	Unweighted mean *r* (95% CI)	Standardized OR (95% CI)[a]	λ weight	Moderator analysis[b]	
					Fixed	Random
Participant Characteristics						
Female (Percent of sample)	26	.14 (.04, .24)	1.76 (1.17, 2.66)	N/A	N/A[c]	$r = -.20$
CD4 Count						
less than or equal to median (421 cells/μL)	8	.27 (−.01, .50)	3.03 (0.96, 9.00)	+1	$Z = 3.78^{***}$	$r = .39^{\dagger}$
greater than median	8	.06 (−.08, .20)	1.27 (0.73, 2.25)	−1		
Depression Severity						
Clinical depression (diagnosis or moderate severity)	15	.21 (.06, .35)	2.35 (1.27, 4.31)	+1	$Z = 3.72^{***}$	$r = .30^{\dagger}$
No inclusion criteria for depressive symptoms	14	.07 (−.01, .16)	1.15 (0.98, 1.38)	−1		
Depression Treatment Moderators						
Treatment Objective						
Depression treatment is primary objective	16	.23 (.10, .36)	2.55 (1.49, 4.52)	+1	$Z = 5.20^{***}$	$r = .43^{**}$
Depression treatment is secondary objective	13	.04 (−.05, .13)	1.17 (0.82, 1.69)	−1		
Integration with Adherence Training						
Treatment integrated with adherence training	10	.13 (.00, .25)	1.69 (1.00, 2.78)	+1	$Z = 0.01$	$r = .001$
No adherence training	7	.13 (−.27, .49)	1.69 (0.33, 8.54)	−1		
Treatment Duration						
At least 17 sessions or weeks	6	.28 (−.13, .61)	3.16 (0.59, 17.04)	+1	$Z = 4.76^{***}$	$r = .43^{*}$
9 to 16 sessions or weeks	7	.18 (.00, .35)	2.07 (1.00, 4.31)	0		
Up to 8 sessions or weeks	11	.03 (−.06, .11)	1.13 (0.79, 1.56)	−1		
Psychotherapy Format						
Individual psychotherapy	8	.14 (−.04, .31)	1.76 (0.85, 3.60)	+1	$Z = 2.67^{**}$	$r = .41^{\dagger}$
Group psychotherapy	7	.00 (−.10, .10)	1.00 (0.67, 1.49)	−1		
Methodological Moderators						
Study Design						
Observational	12	.17 (.13, .21)	1.99 (1.69, 2.35)	+1	$Z = 2.99^{***}$	$r = .33^{*}$
Randomized controlled trial	15	.07 (−.03, .17)	1.32 (0.89, 1.99)	−1		

Moderator	No. of studies	Unweighted mean *r* (95% CI)	Standardized OR (95% CI)[a]	λ weight	Moderator analysis[b] Fixed	Moderator analysis[b] Random
Comparison Group						
Standard care or wait-list control	19	.14 (.01, .26)	1.76 (1.04, 2.90)	+1	$Z = 0.03$	$r = .002$
Informational/psychoeducational program	6	.13 (−.10, .35)	1.69 (0.67, 4.31)	−1		
Sample Size						
Greater than the median ($N = 156$)	14	.14 (.09, .18)	1.76 (1.43, 2.07)	+1	$Z = -.38$	$r = -.03$
Less than or equal to the median	15	.15 (−.02, .32)	1.35 (0.96, 1.94)	−1		
Adherence measure						
Subjective (self-report)	20	.12 (−.01, .24)	1.62 (0.96, 2.66)	+1	$Z = -2.65^{**}$	$r = -.19$
Objective (pharmacy data or electronic pill cap)	9	.21 (.12, .30)	2.35 (1.62, 3.45)	−1		

[a] Standardized odds ratios and confidence intervals were calculated from the average effect size *r* using the binomial effect size display (31).

[b] Significant values indicate that the association between depression treatment and ART adherence differ based on the moderating variable.

[c] The fixed effects moderator analysis can only be conducted for categorical variables, not continuous variables.

All *p* values are one-tailed:

$^{***}p \leq .001$,

$^{**}p \leq .01$,

$^{*}p \leq .05$,

$^{\dagger}p \leq .10$