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Depression and HIV/AIDS Treatment Nonadherence: A Review and Meta-analysis

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Abstract

We meta-analyzed the relationship between depression and HIV medication nonadherence to calculate the overall effect size and examine potential moderators. Overall, across 95 independent samples, depression was significantly ($P < 0.0001$) associated with nonadherence ($r = 0.19$; 95% confidence interval = 0.14 to 0.25). Studies evaluating medication adherence via interview found significantly larger effects than those using self-administered questionnaires. Studies measuring adherence along a continuum found significantly stronger effects than studies comparing dichotomies. Effect size was not significantly related to other aspects of adherence or depression measurement, assessment interval (ie, cross-sectional vs. longitudinal), sex, IV drug use, sexual orientation, or study location. The relationship between depression and HIV treatment nonadherence is consistent across samples and over time, is not limited to those with clinical depression, and is not inflated by self-report bias. Our results suggest that interventions aimed at reducing depressive symptom severity, even at subclinical levels, should be a behavioral research priority.

Keywords

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

Introduction

Strict adherence to highly active antiretroviral therapy (HAART) remains a challenge that has important implications for treatment success. Although resistance profiles are regimen dependent, nonadherence is associated with increased risk of treatment failure and viral resistance.[1–4] Therefore, identifying modifiable factors associated with treatment

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nonadherence and developing appropriate interventions to improve adherence and health outcomes in patients with HIV/AIDS remains an important goal of behavioral science research.

Depressive symptoms are common among individuals living with HIV/AIDS; nationally representative data suggest that 36% of these individuals are likely to screen positive for clinical depression.[5] Depressive symptoms, that do not necessarily meet criteria for a depressive disorder, have also been linked to worse HIV health outcomes, including impaired immunological response and mortality.[6–12] Treatment nonadherence may be one potential pathway to explain the relationship between depressive symptoms and worse outcomes in HIV/AIDS. Though causal evidence for this relationship is elusive, it is highly plausible that depressive symptoms, such as loss of interest, diminished concentration, feelings of worthlessness, and recurrent thoughts of death would be disruptive to the self-management activities required by HIV treatment. Although many studies have examined the relationship between depression and treatment nonadherence in patients with HIV/AIDS, these findings have not been analyzed in aggregate.

We surveyed the extensive literature on depression and antiretroviral nonadherence in HIV-infected individuals and performed a meta-analysis of published studies to evaluate the strength and consistency of this association. To better characterize the nature of this relationship, we also examined whether the association between depression and nonadherence varied as a function of several potentially important methodology-related and population-related moderators (described below).

Methods

Literature Search and Inclusion Criteria

We conducted manual reviews of relevant articles, contacted experts in the field, and searched electronic databases (MEDLINE, PubMed, and PsychINFO) to identify articles published between 1996 through February 2010 examining the relationship between depression and treatment adherence in patients with HIV/AIDS. We combined search terms (available upon request) for HIV/AIDS with those for depression, and treatment adherence. Studies were limited to those as follows: (1) published in English in peer reviewed journals; (2) involving children, adolescents, or adults with HIV/AIDS; (3) reporting sufficient data on the strength of the relationship between depression and treatment adherence to calculate an effect size for an unadjusted relationship where individuals were the unit of analysis; and (4) not involving any intervention that could possibly affect the relationship between treatment adherence and depression. Where articles reported insufficient information to calculate an unadjusted effect size but reported a relationship between depression and adherence, we contacted authors for additional data and included data, if provided.

Treatment adherence was operationalized as the taking of prescribed medication for the treatment of HIV/AIDS over a given period including both the percentage and persistence of taking prescribed medication (3 studies conceptualized complete nonadherence over a specified period as therapy discontinuation[13–15]). Depression was operationalized to include studies that used any method of assessing depressive symptoms or diagnosis of a depressive disorder as defined by the *Diagnostic and Statistical Manual of the Mental Disorders (editions III-IV-TR*[16–19]), including self-report measures, interviews, and medical record abstraction for depressive disorder diagnosis.

Data Extraction

After the search was conducted, abstracts were divided in 5 parts and reviewed by 5 coders who were trained and supervised by the primary author (J.S.G.). Each abstract list received at least 3 independent reviews by these coders. When unclear, final determinations about inclusion/exclusion were made by the primary author (J.S.G.). In addition to the information needed to compute effect sizes, each article was coded according to the methods used to assess adherence and depression, the design of the study (cross-sectional vs. longitudinal), the percentage of females, injection drug users (IDUs), and men who have sex with men (MSM) in the sample, and the country in which the study was conducted.

To ensure independent effects, each sample contributed only one effect size to the meta-analysis. When data from the same sample was reported in multiple publications,[20–24] we selected the study with the larger sample that focused on individual-level data, rather than visit pairs as the unit of analysis.[25] When relationships between depression and adherence were reported for discrete subgroups within 1 study, groups were included as independent samples.[26] When multiple types of adherence were reported, we took the average of the reported effects and treated this effect as reflective of a composite.[27–29] However, when several different quantifications of the same measurement type were available, we selected the effect based on stronger methodology (eg, we selected continuous measures when data on both continuous and dichotomized relationships were reported). If sample sizes differed for different measures, we used the measures that had a larger sample size.[14,15,30] If a study included samples of the same size over differing amounts of time, the longest amount of time was selected (eg, 1-month period rather than 3-day period).[22,31,32] If a study reported more than 1 cut-off for adherence, the more extreme cut-off was used (eg, 100% vs. 90%).[33] One study reported both data for depression and dysthymia; we used the depression data only.[34] One study reported depression data with and without somatic symptoms; we chose the data without somatic symptoms.[35] One excluded study evaluated mood disorders but did not differentiate between depressive disorders and other mood disorders;[36] inclusion did not alter our overall findings or the results of moderation analyses.

Statistical Analysis

We followed the meta-analytic procedures of Lipsey and Wilson[37] and Borenstein et al.[38] The effect size *r* was used to quantify the continuous relationship between depression and nonadherence. When *r* or phi statistics were not provided, we computed *r* from means and *SDs*, odds ratios, *t* tests, χ^2, *F*, contingency table data, or exact *P* values. When means and SDs were reported for more than 2 groups (eg, adherence scores for low, intermediate, and high depression), we based our effect size calculations on comparisons between the most extreme groups.[39] When studies presented effect sizes that had more than 1 degree of freedom, we contacted authors to obtain bivariate data. However, because it has been demonstrated that *r* can be accurately estimated from beta coefficients in multiple regression, even when covariates are present, we estimated *r* in one case[40] using the formula $r = 0.98\beta + 0.05\lambda$, where λ is an indicator variable that equals 1 when β is nonnegative and 0 when β is negative.[41] As general estimating equation logit models use similar assumptions about the underlying distribution of data as logistic regression models, an odds ratios based on the GEE logit model was used to calculate an estimated r value for one study.[42]

We report effect sizes based on the random effects model and used a fully random effects analysis to examine moderators. Effect sizes are weighted by the inverse variance of each study, which is determined primarily by sample size but also takes account of other factors that affect the precision of the ES.[37] All computations were based on Fisher *Z* transformations of *r*. Meta-analytic software (Comprehensive Meta-Analysis 2.0) was used to calculate average *Z* scores, and *P* values, weighted ES *r-values*, and the 95% confidence

interval around the collective ES values. Variability among effect sizes was evaluated by the *Q* statistic and the *I*-squared index, which serves as a ratio of the variance between studies to total variance.[43] We also calculated the "fail safe n" for each grouped ES,[44] reflecting the number of unpublished studies necessary to reduce the obtained ES to nonsignificance. Cohen[45] has suggested that, in behavioral science research, effects can be considered small when $r \leq 0.10$, medium when $r = 0.25$, and large when $r \geq 0.40$.

Moderation Analyses

We also examined whether the effect size differed significantly across levels of potential moderators of the depression-adherence relationship using random effects models. First, we evaluated the moderating effect of adherence measurement in several a priori comparisons as follows: (1) electronically monitored vs. self-report, (2) objectively collected (electronically monitored and pharmacy refill data) versus self-report, and (3) interview versus noninterview self-reports. Second, we evaluated whether the measurement of methods for depression moderated the relationship as follows: (1) structured clinical interview for diagnosis of clinical depression versus self-report of depressive symptoms and (2) diagnosis-based assessment (interview-based or medical record–based strategies that focused on identification of clinical depression) versus symptom-based assessments. We also examined study design as a potential moderator by comparing studies that evaluated the relationship between adherence and depression cross-sectionally to those that evaluated longitudinal relationships. We next examined whether the observed effect size varied between studies conducted in resource-rich countries (ie, United States, Australia, Canada, Western Europe, Hong Kong, and Puerto Rico) versus those conducted in resource-limited countries (ie, Ethiopia, India, and Peru). Finally, we examined the potential influence of participant characteristics on the observed effect size by calculating slopes via meta-regression and the method of moments estimate for the following factors: (1) percentage of female participants, (2) percentage of IDUs, and (3) percentage of MSM.

Results

Overall Analysis

A total of 95 independent study samples, including 35,029 participants from 95 published reports, met our inclusion criteria. The characteristics and findings of these studies are summarized in a supplemental table, available online (see online appendix of Supplemental Digital Content 1, http://links.lww.com/QAI/A214, which lists characteristics of the 95 included studies). The studies used a variety of measures, methods, samples, and analytical approaches. Overall, meta-analysis revealed a significant association between depression and antiretroviral adherence ($Z = 6.79$, $P < 0.0001$) and a weighted ES $r = .19$ (95% confidence interval = .14 to 0.25). The heterogeneity statistics indicate a lack of significant heterogeneity in this effect ($Q = 33.58$, $I^2 = 0.00$). The "failsafe n" for the number of unpublished studies with null findings required to bring this effect to nonsignificance is 19,256.

Moderation Analyses

Table 1 shows that moderation analyses focused on methods of adherence assessment suggested a nonsignificant trend ($P = 0.09$) for stronger relationships between depression and electronically-monitored adherence than for depression and self-reported adherence. Studies that measured adherence by interview found a significantly ($P = 0.03$) stronger effect between depression and nonadherence than studies that measured adherence by self-completed questionnaire (paper-and-pencil or computer administered). Studies that analyzed adherence as a continuous variable found significantly ($P = 0.02$) stronger effects than studies that evaluated adherence as a categorical variable (nonadherent vs. adherent).

Table 1 also shows that there was no evidence to suggest a moderating effect of depression measurement: diagnosis based studies did not differ from studies that evaluated symptoms of depression and categorical comparisons (eg, high vs. low depression) were not more likely to find larger relationships with adherence than studies that evaluated depression symptom severity along a continuum. There was also no difference between studies that evaluated the relationship between depression and adherence cross-sectionally and those that evaluated the relationship over time. Table 1 also shows that there was no difference in the effect sizes of studies from the high-resource versus resource-limited settings. Finally, none of the slopes for participant characteristics (sex, IDU, MSM) were significant in meta-regression (data not shown).

Discussion

The results of this meta-analysis, based on 95 independent samples totaling more than 35,000 patients, suggest that depression is consistently associated with nonadherence to HIV treatment with an effect of small to moderate strength. The size of this overall effect (r = 0.19) is similar to the effect (r = 0.21) obtained by a meta-analysis of depression and treatment nonadherence based on 12 studies of patients with other chronic illnesses.[46] It is also similar in magnitude to the effect (r = 0.21) obtained by a recent meta-analysis examining the relationship between depression and diabetes treatment adherence.[47]

Moderation analyses focused on HAART adherence assessment methods demonstrated a significantly stronger effect (r = 0.26) in studies that analyzed medication adherence as a continuous variable than studies that evaluated adherence as a categorical variable. This is consistent with evidence demonstrating that artificial dichotomization of continuous variables reduces power and accuracy of analyses[48] and suggests that the true effect for depression and HAART nonadherence may be of medium strength, according to Cohen benchmarks.[45] Among approaches that relied on patient reports of nonadherence, studies that assessed medication adherence via interview found a significantly stronger effect (r = 0.22) than studies that evaluated adherence based on patient-completed self-report. Importantly, studies measuring adherence via electronic caps found stronger effects than those relying on patient completed self-reports, although the difference was short of significance. Moreover, when objective measures of adherence were compared with methods relying on subjective reports, we found no difference in effects. This consistency across objective and subjective assessments is important given a strong literature demonstrating biased memory for negative information in depressed individuals,[49] which suggests the possibility that depression may result in an overestimate on nonadherence by patient report. We found no evidence to support this possibility.

These findings are consistent with previous research that found *improved* concordance (of borderline significance, P = 0.07) between self-reported and electronically monitored adherence to medications for heart failure and hypertension in depressed patients as compared with patients who were not depressed.[50] Furthermore, the results of a meta-analysis of the literature on depression and diabetes treatment nonadherence also found significantly stronger relationships when adherence was measured by objective methods (eg, electronic data on frequency of glucose monitoring) than when measured via self-report.[47] Finally, a study recently published (thus, not included in the meta-analysis), observed a strong effect (Cohen d = 0.98) between depressive symptom severity and HAART nonadherence in a sample of HIV-infected patients in methadone maintenance using measurement procedures that controlled for reporting biases; depression severity was assessed by structured clinical interview, and medication adherence was assessed by electronic pill caps.[51] Taken together, these findings provide strong evidence that the

consistent relationship between depression and HIV-treatment nonadherence is not an artifact of self-report methods or due to the negative recall bias associated with depression.

Our findings also suggest that the relationship between depression and HAART nonadherence is not limited to comparisons between those who meet criteria for clinical depression and those who do not; studies that focused on depression diagnosis found equivalent effects to studies that measured depression as a degree of symptom severity. This is consistent with work we have conducted in diabetes patients that demonstrates an incremental association between depression symptom severity and treatment nonadherence, even in patients unlikely to meet the criteria for diagnosis.[52] We also found a strong incremental relationship between depression symptom severity and electronically monitored nonadherence in a sample of HIV-infected patients in methadone maintenance, even though our sample reported relatively high levels of depression severity overall. Diagnosis of a depressive disorder was not associated with adherence.[51] Thus, these findings suggest an incremental relationship between symptoms of depression and risk for treatment non-adherence, observable at both lower and higher levels of depression severity, and do not support the notion that depression only becomes a risk factor for nonadherence when it reaches the threshold for a clinical diagnosis.

Our results should be considered in the context of several important limitations of the literature. First, the causal nature of this relationship is not clear given the difficulty of applying experimental designs—all of the reviewed studies were correlational. The directionality of this relationship is also unclear. Research has suggested the possibility that effective adherence to HAART could reduce amino acids that are involved in the production of serotonin and dopamine.[53,54] The serotonin precursor, tryptophan, in particular, has been associated with both immune activation and depression severity in HIV-infected patients.[55] Thus, it is plausible that successful adherence to HAART could contribute to reduced depression through physiological pathways.

Second, although many studies have examined “whether” depression is associated with treatment nonadherence in HIV/AIDS, none of the included studies examined “how” depression is related to nonadherence. Plausible explanations may relate to the symptoms of depression themselves. For example, we reported large differences in depression-associated concentration difficulties and appetite disturbance between nonadherent and adherent patients taking HAART[51]; these symptoms may directly interfere with medication taking. Several studies, though not directly examining depression, per se, have examined other potential mediators of the relationship between distress and nonadherence. One study showed that negative mood states are associated with increased symptom reports and more concerns about the negative effects of HAART.[56] A second found support for a model where avoidant coping mediated the relationship between negative mood states and HAART adherence.[57] Finally, one study examining mediators of the relationship between psychiatric disorder and HAART nonadherence found support for a mediating role for difficulty in obtaining medication and poor fit of the HAART regimen with the patient's lifestyle.[58] More research that examines the potential mechanisms linking depression and treatment nonadherence in HIV/AIDS is necessary to develop more focused interventions.

Finally, our review of the literature also demonstrated that far more attention has been paid to the role of depression in HIV treatment nonadherence than to other psychiatric conditions and subclinical presentations of distress, despite the role of a wider set of mental health factors in HIV outcomes.[59] Stress and trauma, in particular, have been consistent risk factors for HIV disease progression.[60] However, the limited research that has been conducted suggests that depression may often be an important comorbid condition in patients with other psychiatric illnesses. For example, one study showed that depression was more

common in patients screening positive for posttraumatic stress disorder and was uniquely associated with antiretroviral nonadherence while posttraumatic stress disorder was not.[61] Similarly, in our work in HIV-positive patients in methadone maintenance, depression was a unique predictor of HAART nonadherence after controlling for current substance abuse.[51] Thus, disentangling the relationships between psychiatric conditions and nonadherence is likely to require attention to the problem of depression comorbidity.

Interventions designed to treat clinical depression and simultaneously support adherence with cognitive and behavioral skills have found strong evidence for success in improving both depression and treatment adherence outcomes and provide a model for how these inter-related problems can be approached through behavioral intervention.[62] Although research has shown that interventions can also be successful in reducing subclinical depression in HIV, the impact of these interventions on health outcomes is less clear.[63–65] Our results show that the relationship between depression symptoms and nonadherence is stable across populations and is not short lived; cross-sectional studies obtained equivalent effects to those found in longitudinal studies. Thus, as recent work has compellingly demonstrated that inconsistent use of antiretrovirals over time partially explains the relationship between depressive symptoms and HIV disease progression,[66] interventions that target depressive symptoms, *and* optimal utilization of HAART (ie, improved adherence and improved persistence in regularly taking HAART over long periods) may have maximal effects on health outcomes. A variety of community-based and clinic-based studies suggest that a significant proportion (20%–50%) of HIV-infected patients experience such symptoms.[6,12,67–69] The high prevalence suggests that even the relatively modest risk for nonadherence associated with depression identified by the current meta-analysis could have important implications for treatment outcomes at the population level. Novel approaches to the successful management of these linked problems could have significant public health impact for patients living with HIV/AIDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Overall and Moderation Analyses

	n	*Z* (*P*)	Weighted *r*	95% CI	Heterogeneity Q (*df*) and I^2	Fail Safe n (*P* > 0.05)
Overall analysis	95	6.788 (<0.000)	0.192	0.137 to 0.246	33.580 (94); I^2 = 0.000	19,256
Moderation analyses						
Adherence measurement						
Electronic pill cap monitor	6	4.460 (*P* < 0.000)	0.260	0.148 to 0.365	32.768 (5); I^2 = 84.741	56
Self-report	59	9.435 (*P* < 0.000)	0.159	0.127 to 0.192	41.675 (58); I^2 = 0.000	4490
Total between: 2.870 (1), *P* = 0.090						
Pharmacy refill and electronic monitor	13	3.361 (*P* = 0.001)	0.229	0.097 to 0.353	22.732 (12); I^2 = 47.210	1449
Self-report and interview	80	6.581 (*P* < 0.000)	0.184	0.130 to 0.236	18.991 (79); I^2 = 0.000	9135
Total between:0.396 (*df* = 1), *P* = 0.529						
Interview	21	8.241 (*P* < 0.000)	0.223	0.171 to 0.274	17.174 (20); I^2 = 0.000	794
Self-report	59	10.146 (*P* < 0.000)	0.157	0.127 to 0.187	58.000 (58); I^2 = 0.000	4490
Total between: 4.716 (*df* = 1), *P* = 0.030						
Categorical	67	6.056 (0.000)	0.158	0.107 to 0.208	20.181 (66); I^2 = 0.000	5065
Continuous	28	6.569 (0.000)	0.264	0.187 to 0.337	31.929 (27); I^2 = 15.438	4218
Total between: 5.113 (*df* = 1), *P* = 0.024						
Depression measurement						
Diagnostic interview	6	2.496 (*P* = 0.013)	0.134	0.029 to 0.237	6.033 (5); I^2 = 17.117	24
Self-report	83	12.200 (*P* < 0.000)	0.173	0.146 to 0.200	58.053 (82); I^2 = 0.000	9319
Total between: 0.500 (*df* = 1), *P* = 0.480						
Diagnosis	12	3.462 (*P* = 0.001)	0.246	0.108 to 0.374	22.670 (11); I^2 = 51.479	1575
Symptom severity	83	6.491 (*P* < 0.000)	0.181	0.127 to 0.234	17.210 (82); I^2 = 0.000	9319
Total between: 0.749 (*df* = 1), *P* = 0.387						
Categorical	47	4.909 (*P* < 0.000)	0.192	0.117 to 0.266	28.602 (46); I^2 = 0.000	5877
Continuous	48	4.875 (*P* < 0.000)	1.188	0.113 to 0.261	7.800 (47); I^2 = 0.000	3532
Total between: 0.007 (*df* = 1), *P* = 0.933						
Study design						
Cross-sectional	81	6.365 (0.000)	0.196	0.136 to 0.254	32.078 (80); I^2 = 0.000	14,937

	n	*Z* (*P*)	Weighted *r*	95% CI	Heterogeneity Q (*df*) and I^2	Fail Safe n (*P* > 0.05)
Longitudinal	14	2.143 (0.032)	0.158	0.014 to 0.296	1.832 (13); I^2 = 0.000	190
Total between: 0.236 (*df* = 1), *P* = 0.627						
High vs. low-resource countries						
High-resource countries	90	6.498 (*P* < 0.000)	0.187	0.132 to 0.242	33.187 (*df* = 89); I^2 = 0.000	16,788
Low-resource countries	5	1.987 (*P* = 0.047)	0.243	0.003 to 0.456	1.579 (*df* = 4); I^2 = 0.000	43
Total between: 0.205 (*df* = 1), *P* = 0.650						

CI, confidence interval.