Published in final edited form as:

Ann Behav Med. 2011 August ; 42(1): 120–126. doi:10.1007/s12160-011-9268-y.

Clinician-Assessed Depression and HAART Adherence in HIV-Infected Individuals in Methadone Maintenance Treatment

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Abstract

Background—The impact of measurement methods on the relationship between depression and HIV treatment adherence has not been adequately examined.

Purpose—The purpose of this paper is to examine the relationship between clinician- and patient-rated depression and HIV medication adherence.

Methods—The participants were 91 HIV-infected individuals in methadone maintenance. Depression was assessed via clinician ratings (Clinical Global Impression Scale and Montgomery Asberg Depression Rating Scale) and self-report (Beck Depression Inventory-Short Form). Clinicians rated substance abuse using the Clinical Global Impression Scale and a structured interview. HIV medication adherence was measured over the following 2 weeks using electronic caps.

Results—Each unit increase in the Clinical Global Impression Scale was associated with 75% increased odds of nonadherence (OR=1.75, $p=0.002$, 95% CI=1.23–2.48). Similarly, for each standard deviation Montgomery Asberg Depression Rating Scale increase, there was a 2.6-fold increased odds of nonadherence (OR=2.60, $p=0.001$, 95% CI=1.45–4.67). Substance abuse and self-reported depression severity were not significantly related to adherence.

Conclusions—Clinician-rated depression severity was a strong predictor of nonadherence. Assessment methods may influence the relationship between depression and HIV nonadherence.

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Conflict of interest statement The authors have no conflict of interest to disclose.

Keywords

HIV; Depression; Adherence; Assessment; Methadone maintenance; HAART

Introduction

The widespread use of highly active antiretroviral therapy (HAART) has drastically improved the treatment outcomes for those living with HIV/AIDS [1]. However, even occasional nonadherence to HAART is associated with treatment failure [2]. Depression may be one of the more important patient-level factors that influence treatment adherence, with a meta-analysis of 12 studies of chronic illness patients showing that depressed patients are three-times more likely to be non-adherent as nondepressed patients [3]. While this meta-analysis did not include HIV+ individuals, almost half (48%) of those living with HIV have symptoms of depression, according to nationally representative data [4]. Research examining the association of depression and HAART adherence has been inconsistent in the measurement of depression and adherence and has yielded somewhat mixed results.

Studies have found that those meeting the diagnostic criteria for clinical depression have poorer self-reported HAART adherence than those who did not (e.g., [5]). However, other studies suggest that clinical depression is not related to objectively measured [6] or self-reported [7] HAART adherence. The evaluations of depression on a continuum of symptom severity have almost exclusively relied on self-report measures but most have found a relationship with HAART nonadherence (e.g., [8, 9]). One notable study found strong associations between clinician-rated depression severity and self-reported HAART nonadherence in an Italian sample of HIV-infected adults [10].

Individuals with a history of injection drug use are one of the largest groups of individuals living with HIV in the U.S. and may be particularly at risk for both nonadherence and depression. Investigations of the relationship between depression and HAART adherence among injection drug users have produced inconsistent findings; some studies have found a relationship between self-reports of depression severity and HAART adherence (e.g., [11, 12]), while others have not found a relationship between self-reported depression and electronically monitored adherence [13–15]. This inconsistency suggests the possibility that self-reported measures of HAART adherence are biased by overestimates of nonadherence in depressed patients, perhaps due to the negative self-appraisal patterns [16] or the bias in recall for negative information [17] known to be associated with depression. This possibility is supported by data showing a significant relationship between self-reports for depression and medication nonadherence but not for self-reported depression and electronically monitored nonadherence in patients with heart failure [17]. The current study explored this possibility by evaluating the relationship between depression and HAART adherence among injection drug users using measurements that are not subject to the possible biases associated with self-report from depressed individuals. We hypothesized that more objective measures would yield stronger effects than self-reports.

Methods

Participants

The current data were obtained from baseline evaluations of 91 HIV+ individuals (59% male, 35% Hispanic/Latino, 16% black/African American, 83% heterosexual) in methadone maintenance therapy in the Boston, MA and Providence, RI areas who were screened for participation in a randomized trial of cognitive-behavioral therapy targeting medication adherence and depression. Therefore, the sample was expected to reflect a population that

was experiencing significant symptoms of depression and interested in obtaining treatment. All but seven participants met the criteria for an Axis I disorder (excluding substance abuse and dependence): 55 met the criteria for major depressive disorder; three met the criteria for dysthymia; 21 met the diagnostic criteria for bipolar disorder.

The participants had a mean age of 47 years old ($M=47.16$, $SD=7.04$), an average of 11 years of education ($M=11.26$, $SD=2.77$), and reported being diagnosed with HIV for between 3 and 26 years ($M=16.70$ years, $SD=5.61$). Approximately 4% were engaged in full-time work or education, 8% were engaged in part-time work or attending school part-time, and 73% were on disability. Approximately 67% of the sample had an undetectable viral load (median detectable viral load= 815.50 copies). The mean CD4 count was 426.1 ($SD=236.10$).

The present analysis is limited to patients who: (1) were HIV+ and prescribed HAART, (2) demonstrated a history of injection drug use, (3) were enrolled in methadone maintenance treatment, (4) were between the ages of 18 and 65, and (5) complied with the use of an electronic pill cap to monitor adherence. Patients were excluded from the study if they were currently in cognitive behavioral therapy for depression, had a major mental illness that would interfere with participation, or were unwilling to consent.

Measures

Depression—The Mini International Neuropsychiatric Interview [18], a short structured psycho-diagnostic interview, was administered by a trained clinician to assess mood disorders, alcohol use disorders, anxiety disorders, and psychosis. The Montgomery Asberg Depression Rating Scale [19], a structured clinical assessment of ten commonly occurring symptoms of depression over the past week, measured depression symptom severity. Scores range from 0 to 60: 0–6 indicates no depression, 7–19 indicates mild depression, 20–34 indicates moderate depression, and 35–60 indicates severe depression. Internal reliability was high in the current sample ($\alpha=0.86$). The Clinical Global Impression Scale [20] for severity of depression (1=not ill to 7=extremely ill) was used to measure severity and impairment due to depression, based on clinician evaluation. The Beck Depression Inventory-Short Form [21] was used to assess self-reported depression severity. This 13-item questionnaire has been validated in methadone patients [22] and a score of 13–14 indicates clinical depression (sample $\alpha=0.88$).

Substance Use—The Addiction Severity Index-Lite version is a shortened version of the Addiction Severity Index [22] available from the World Health Organization [23, 24]. It assesses drug and alcohol use in the prior 30 days via a semistructured interview. The current analyses examined drug use and alcohol intoxication as dichotomous variables of any frequency of occurrence within the past 30 days versus no occurrence. Clinicians also completed a Clinical Global Impression Scale rating for substance abuse severity (1=not ill to 7=extremely ill). Participants were ensured of the confidential nature of their responses and were explicitly informed that the information would not be shared with providers at the methadone clinics without their approval.

HAART Adherence—Medication event monitoring system (electronic caps; AARDEX, Zurich, Switzerland) caps were employed to assess adherence over a 2-week period following the assessment of depression and substance abuse severity. The electronic caps were used to monitor the HAART medication that patients took most frequently or found to be most difficult to remember. The percent of doses taken as prescribed was calculated by dividing the number of times the bottle was opened by the number of times it should have been opened as per the prescription. If the participants could remember specific times that

they took their pills but knew they did not use the electronic cap, corrections were allowed for “pocketed” doses.

Procedure

All study procedures were approved by the institutional review boards at Massachusetts General Hospital, Boston, MA and at Rhode Island Hospital, Providence RI. Doctoral level psychologists or pre- or post-doctoral psychology fellows who were blind to the collected adherence data completed the Mini International Neuropsychiatric Interview, Montgomery Asberg Depression Rating Scale, Addiction Severity Index-Lite, and Clinical Global Impression Scale ratings. Extensive training on all relevant measures was provided, and all study assessors participated in weekly supervision during which audio files of assessment visits were reviewed to ensure the quality and accuracy of the procedures. At the first study visit, the participants provided informed consent and demographic information; the independent clinician assessed depression severity and the study staff instructed the participants on the use of the electronic caps. At the second study visit, approximately 2 weeks later, participants completed the self-report battery and provided electronic cap data.

Data Analysis

All data were analyzed using SPSS 17 (SPSS Statistics 17.0.0., Chicago, IL). Data were examined for skewness and kurtosis. As electronic monitoring cap data were not normally distributed, and based on the clinical importance of even occasional HAART nonadherence in the management of HIV/AIDS [2], adherence analyses compared those who had missed any doses over the relevant time frame to those who had not. Patient sex, ethnicity, age, employment status, education, drug use/alcohol intoxication, and substance abuse measured using the Clinical Global Impression Scale were examined as potential covariates that would be included in multivariate analyses based on a trend-level relationship ($p < 0.10$) with adherence. Initial comparisons between adherent and nonadherent participants on each depression measure were conducted using independent t tests. The mean differences were divided by the pooled standard deviation to calculate Cohen's d effect sizes for the differences between adherent and nonadherent participants in depression severity where $d = 0.20$, 0.50 , and 0.80 would indicate a small, medium, and large effect, respectively [25]. To examine which symptoms of depression were associated with nonadherence, adherence groups were also compared on the individual items from the Montgomery Asberg Depression Rating Scale using t tests. Finally, logistic regression was used to predict nonadherence from the Montgomery Asberg Depression Rating Scale total, Clinical Global Impression Scale for depression, and the Beck Depression Inventory-Short Form total score where the Montgomery Asberg Depression Rating Scale and Beck Depression Inventory-Short Form scores were converted to Z scores to facilitate the comparison.

Results

Depression Severity and Substance Abuse

The average depression score on the Montgomery Asberg Depression Rating Scale was in the moderate severity range ($M = 24.27$, $SD = 11.38$). The average Clinical Global Impression Scale score for depression corresponded to, “moderately ill” ($M = 4.05$, $SD = 1.66$; range = 1–7). The mean score on the Beck Depression Inventory-Short Form was 11.51 ($SD = 6.90$), below the cutoff for clinical depression. The Beck Depression Inventory-Short Form was significantly correlated with the Montgomery Asberg Depression Rating Scale total score ($r = 0.56$, $p < 0.001$) and depression Clinical Global Impression Scale score ($r = 0.61$, $p < 0.001$), but the Montgomery Asberg Depression Rating Scale and Clinical Global Impression Scale ($r = 0.89$, $p < 0.001$) were more strongly correlated with each other than the Beck Depression Inventory-Short Form and Clinical Global Impression Scale (Dunn and Clark $z = -5.61$,

$p < 0.0001$) or the Beck Depression Inventory-Short Form and Montgomery Asberg Depression Rating Scale (Dunn and Clark $z = -6.66$, $p < 0.0001$). The Addiction Severity Index-Lite data showed that only 3% of the participants reported alcohol intoxication in the past 30 days. However, 75% of participants reported using at least one illicit substance in the past 30 days: 46% endorsed using benzodiazepines, 32% used cocaine, 24% used heroin, and 24% used other opiates. Further, almost 40% of the participants reported polysubstance use, not including alcohol. The average Clinical Global Impression Scale score for substance abuse corresponded to, "borderline ill" ($M = 2.11$, $SD = 1.31$; range = 1–6).

Nonadherence and Depression Severity

Electronic cap data revealed an average of 68% of doses taken over 2 weeks ($M = 67.67$, $SD = 28.55$), with less than 20% ($N = 18$) of the sample taking all prescribed doses. The mean differences between adherent and nonadherent participants were significant for depression using the Clinical Global Impression Scale and Montgomery Asberg Depression Rating Scale total scores and corresponded to large effect sizes based on Cohen's benchmarks (See Table 1). Differences in depression as measured by the Beck Depression Inventory-Short Form total score were not significant. An item-level examination of the Montgomery Asberg Depression Rating Scale severity ratings showed that the comparisons between the adherent and nonadherent patients were significant on seven out of 10 Montgomery Asberg Depression Rating Scale items, with patients who were adherent to HAART over the monitoring period scoring consistently lower on symptom severity than those who were nonadherent. The largest mean difference was observed for concentration difficulties (M difference = 1.53, $p = 0.002$). Other relatively large differences were observed for tension/anxiety (M difference = 1.28, $p = 0.002$), appetite (M difference = 1.29, $p = 0.007$), and inability to feel (M difference = 1.28, $p = 0.008$; see Fig. 1). No Beck Depression Inventory-Short Form item-level differences were significant (all p s > 0.166).

Women (10.8%) were less likely than men (25.9%) to be adherent ($\chi^2 = 3.16$; $p = 0.075$) over the monitoring period. Drug use, the Clinical Global Impression Scale for substance abuse, alcohol intoxication, and all other potential covariates were not significantly related to adherence. Thus, sex was added as a covariate in the logistic regression analyses predicting nonadherence. These models showed that each one-point increase in depression Clinical Global Impression Scale score was associated with a 75% increased odds of nonadherence ($OR = 1.75$, $p = 0.002$, 95% $CI = 1.23$ – 2.48). Similarly, for each standard deviation increase in the Montgomery Asberg Depression Rating Scale total Z score, there was more than a 2.5-fold increase in the odds of HAART nonadherence ($OR = 2.60$, $p = 0.001$, 95% $CI = 1.45$ – 4.67). In contrast, the Beck Depression Inventory Z score was not significantly related to adherence ($OR = 1.45$, $p = 0.211$, 95% $CI = 0.81$ – 2.60). Comparisons based on the diagnosis of major depressive disorder, any mood disorder, and any Axis I disorder yielded no significant relationships with adherence (data not shown).

Discussion

The current study evaluated the role of measurement methods in assessing the relationship between depression symptom severity and HAART adherence among a sample of depressed HIV+ adults who, though currently enrolled in methadone maintenance, exhibited significant current drug use. Self-reported depression was not associated with objectively assessed adherence, in contrast to previous studies that found relationships between both the full version of the Beck Depression Inventory [8, 9] and a subset of items that excludes the somatic symptoms [8] and self-reported adherence in HIV. Research has suggested that the relationship between self-reported depression severity and medication nonadherence may reflect a bias associated with self-reported methods [17] and previous reports have suggested a lack of a relationship between self-reported depression severity and HAART adherence

measured using electronic caps in patients on methadone maintenance [12, 13]. However, we found significant relationships with large effect sizes between two measures of clinician-rated depression severity and objectively assessed HAART adherence. When considering the interpretation of these conflicting findings, it seems that measurement methods have important implications. Although our review of the literature showed that self-report measures are the most common method used to evaluate depression in HIV-infected patients in general and in those patients with substance abuse histories in particular, our results suggest that such measures may not adequately capture depression symptom severity, especially in relation to nonadherence. Specifically, we found that the Beck Depression Inventory-Short Form scores shared only 31% and 37% of their variance with the Montgomery Asberg Depression Rating Scale and depression Clinical Global Impression Scale scores, respectively; while the Montgomery Asberg Depression Rating Scale scores were strongly related to nonadherence, the Beck Depression Inventory-Short Form was not. It is possible that Beck Depression Inventory-Short Form items relating to concerns about physical appearance, inability to work, and feeling tired could have resulted in confounding with HIV disease severity to a greater extent than items on the Montgomery Asberg Depression Rating Scale and may have influenced our results. However, while individual item scores on the Montgomery Asberg Depression Rating Scale were consistently related to nonadherence with seven of 10 items reaching statistical significance, no item from the Beck Depression Inventory-Short Form was significantly related to nonadherence.

Examination of item-level differences on the Montgomery Asberg Depression Rating Scale revealed several interesting findings. First, although a significant difference was found on the “Apparent Sadness” item (an item that asks the assessor to rate the degree to which a patient appears sad and depressed) patient-reported sadness (as measured by the “Reported Sadness” item) was not significant. This item-level difference mirrors the overall difference found in our results using clinician-rated depression versus self-reported depression. Second, the largest difference was found for concentration difficulties. This could suggest that a reduced concentration is an important component of the relationship between depression and nonadherence in this population. Anhedonia and tension/anxiety, perhaps reflecting worry-related avoidance, may be important emotional components of depression. Finally, reductions in appetite may be particularly problematic for HAART adherence given that medications are often prescribed to be taken with food and can cause gastrointestinal side effects.

In psychiatric studies of depression in the context of clinical trials, clinician-rated depression is considered the “gold standard” measurement. However, our review of the literature located only one other study of the relationship between depression and HIV treatment nonadherence that employed a clinician-rated measure of depression, which also found a large effect between depression and self-reported nonadherence [10]. Importantly, the sample from this study did not exhibit elevated depression levels. The mean Montgomery Asberg Depression Rating Scale score was 12.29, which is half the level of depression severity found in the current sample. That we were able to detect a relationship between depression symptom severity and nonadherence in this sample where the majority of participants met diagnostic criteria for major depressive disorder suggests that the incremental relationship between depression severity and nonadherence exists even at relatively severe levels of clinical impairment. Thus, it appears that the relationship between depression and treatment nonadherence in HIV-infected methadone patients is better characterized as an incremental relationship based on depression symptom severity than a categorical relationship based on the presence or absence of a depressive disorder.

Our results should be considered within the context of our study design. First, this was a cross-sectional study, and questions of directionality and causality in the reported

relationships could not be adequately evaluated. Our sample was also relatively small and not representative of the general population of HIV-infected patients in methadone treatment because we recruited patients who were interested in obtaining treatment for depression. The high levels of depression severity in this sample may have affected our ability to detect a difference in adherence between those who met the criteria for a depression diagnosis and those that did not. Also, we did not systematically assess for the use of psychiatric medication and were unable to examine the role of antidepressant medication in our analysis. Finally, although our use of electronic caps represents one of the more objective approaches to the measurement of medication adherence, we captured only 2 weeks of adherence data. Although nonadherence of any magnitude has important implications for the treatment success in HIV [2], whether depression severity predicts adherence over longer periods of time and whether this relationship may account in part for the relationship between depression and worse health outcomes in patients with HIV/AIDS deserves further empirical investigation.

Our results clearly show the clinical importance of the evaluation of depression for identifying those who may be at risk for nonadherence. For every one-point increase on the seven-point depression Clinical Global Impression Scale, for which clinicians made a rating that took into account the overall level of impairment associated with depression symptoms, there was a 75% increase in the odds of HAART nonadherence. Thus, a rating of moderately ill on the Clinical Global Impression Scale, the mean level of impairment in this sample, would confer more than a fivefold increase in the odds of nonadherence as compared to a patient with no evidence of impairment due to depression. The ability of such global clinical ratings of depression to predict future nonadherence deserves empirical evaluation. Although questions regarding causality remain, the strong relationship between problems with depression and treatment nonadherence among individuals with HIV/AIDS in methadone maintenance suggests novel approaches to comprehensive treatment are needed. Interventions that successfully address the co-occurring problems of depression and treatment nonadherence in these patients could have quality of life and health benefits.

Acknowledgments

The funding for this project is from grant R-01DA018603 awarded to Dr. Steven Safren.

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Fig. 1.

Montgomery Asberg Depression Rating Scale item-level differences between adherent and nonadherent groups. Significant differences based on independent groups *t* tests are denoted by asterisks. * $p < 0.05$ ** $p < 0.01$

Table 1

Differences in depression severity between adherent and nonadherent patients

	<u>Nonadherent (n=73)</u>		<u>Adherent (n=18)</u>		<u>Analysis</u>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>P</i>	Cohen's <i>d</i>
Montgomery Asberg Depression Rating Scale	26.33	9.73	15.94	13.88	0.007	0.98
Clinical Global Impression Scale	4.36	1.44	2.83	1.98	0.006	0.98
Beck Depression Inventory-Short Form	12.26	6.45	9.88	7.96	0.194	0.35