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Improvements in Depression and Changes in Fatigue: Results from the SLAM DUNC Depression Treatment Trial

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Abstract

Fatigue and depression are common co-morbid conditions among people with HIV infection. We analyzed a population of HIV-infected adults with depression, who were enrolled in a depression treatment trial, to examine the extent to which improvements in depression over time were associated with improvements in HIV-related fatigue. Data for this analysis come from a randomized controlled trial to evaluate the effectiveness of improved depression treatment on antiretroviral adherence. Fatigue was measured using the HIV-Related Fatigue Scale, and depressive symptoms were measured with the Hamilton Depression Rating Scale. Participants (n = 234) were on average nearly 44 years of age and predominantly male, black or African American, and unemployed. Individuals who experienced stronger depression response (i.e., greater improvement in depression score) had larger decreases in fatigue. However, even among those who demonstrated a full depression response, nearly three-quarters continued to have either moderate or severe fatigue at 6 and 12 months.

Keywords

Depression; Fatigue; Intervention; Syndemic

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Author contributions Study concept and design: Barroso, Gaynes, Quinlivan, Heine, Thielman, Pence. Statistical analysis: Bengtson, Pence. Drafting of the manuscript: Barroso, Bengtson, Pence. Critical revision of the manuscript for important intellectual content: All authors. The senior author (BWP) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with Ethical Standards

Conflicts of interest The authors report no conflicts of interest.

Introduction

Fatigue is a debilitating and ubiquitous symptom among people living with HIV [1]. Prevalence estimates for fatigue range from 33 to 88 % [2], and for those with fatigue, almost 50 % report it as their most debilitating symptom [3]. For people living with HIV, fatigue hampers daily activities, as well as mental function and the ability to socialize. As the number of people living with HIV long-term continues to increase, strategies to effectively manage fatigue are increasingly important.

Among HIV-infected individuals, fatigue is often comorbid with a range of psychosocial factors including depression, anxiety, and post-traumatic stress disorder [2]. Of these, depression is perhaps the most prevalent, affecting 20–30 % of HIV-infected individuals [4–6]. Depression has been consistently and strongly associated with HIV-related fatigue [2, 7–19]. The high co-occurrence of fatigue and depression can be explained in part by the fact that fatigue is one of the nine core symptoms of major depressive disorder [20]. However, HIV-related fatigue has been described as a condition clinically distinct from depression [21–23]. Thus effective depression treatment might be expected to partially ameliorate but not fully resolve HIV-related fatigue.

In the present study, we analyzed a population of HIV-infected adults with depression, who were enrolled in a depression treatment trial, to examine the extent to which improvements in depression over time were associated with improvements in HIV-related fatigue.

Methods

Data for the present analysis come from a randomized controlled trial to evaluate the effectiveness of improved depression treatment on antiretroviral adherence (the SLAM DUNC Study), described in detail elsewhere [24]. Briefly, HIV-infected patients receiving medical care at one of four US infectious disease clinics were eligible to participate if they were English speaking, ages 18–65, screened positive for depression on the Patient Health Questionnaire-9 (score ≥10) [25], and were confirmed to have current major depressive disorder on the Mini International Neuropsychiatric Interview (MINI) [26]. Exclusion criteria included history of bipolar or psychotic disorder, failure of two or more adequate antidepressant trials in the current major depressive episode, or psychiatric presentation requiring immediate hospitalization or other acute intervention [24]. Eligible individuals who agreed to participate were randomized to receive either enhanced usual care for depression or a depression treatment model called measurement-based care (MBC) [27]. In the intervention (MBC) arm, a clinically supervised depression care manager (DCM) provided evidence-based antidepressant treatment recommendations to the HIV provider, who made final decisions on the depression treatment plan. DCM recommendations focused on initiation of antidepressants and dose adjustment based on algorithm-centered depressive symptom response and tolerability, but the HIV provider made all final decisions about treatment. Participants randomized to the enhanced usual care arm could have also received depression treatment from their HIV provider or other sources, but no in-clinic decision support was provided by the DCM. All participants provided written informed consent, and

ethical approval was provided by Duke University, the University of North Carolina at Chapel Hill, and the University of Alabama at Birmingham.

Measures

Fatigue intensity, the primary outcome for this analysis, was assessed at baseline, 6, and 12 months with the Fatigue Intensity subscale of the HIV-Related Fatigue Scale [10,28]. This 8-item subscale includes Likert scale-rated items such as the respondent's level of fatigue today and most days, the severity of the fatigue, and the extent to which fatigue has caused problems or distress. The summary score can range from 1 to 10. This scale has been previously reported to have high internal consistency (Cronbach's alpha = 0.93) [28]; in this sample Cronbach's alpha was 0.92. A binary version of the summary score was used as a secondary outcome, in which individuals were classified as having no fatigue (answers of 1 or 2 on first 7 questions) or any fatigue (summary score >2). Descriptively we also assessed fatigue as a categorical measure, in which individuals were classified as no fatigue, moderate fatigue (summary score <7), or severe fatigue (summary score ≥7) [29]. The 3-level measure of fatigue was not assessed in multivariable analyses due to limited sample size.

Change in depressive severity, the exposure of interest for this analysis, was defined as the relative change in depressive symptom severity at 6 and 12 months, compared to baseline, on the Hamilton Depression Rating Scale (HAM-D) [30, 31], which was administered by trained assessors blinded to study arm. Cronbach's alpha for the HAM-D total score in this sample was 0.83. The change between baseline and 6 or 12 months was categorized into clinically meaningful response categories [32]: full response (≥50 % improvement), partial response (25–49 % improvement), and no response (<25 % improvement). Categorization of change in depression may enhance clinical interpretability but at the cost of precision; continuous measures generally yield narrower confidence intervals and greater statistical power. Thus, we also considered percent change in depressive severity from baseline to 6 and 12 months as a continuous measure.

Potential confounders of interest were identified based on subject matter knowledge and included baseline age, coping style, self-efficacy, number of contacts per quarter with mental health professionals, and baseline psychiatric comorbidities. Coping styles were assessed using the Brief COPE [33, 34] and were collapsed into two summary scales representing adaptive (positive reframing, using emotional support, acceptance, religion, active) and maladaptive (denial, self-blame, behavioral disengagement, substance use) coping strategies, as we have done in prior research [35]. The two scales each ranged from 1 to 4, had high internal consistency (α = 0.80 and 0.74 respectively), and showed low correlation (correlation coefficient 0–0.14), supporting their conceptualization as two distinct factors. Self-efficacy was assessed using the HIV Self-Efficacy questionnaire [36] which contains 6 subscales. The self-efficacy in management of fatigue subscale was eliminated because of overlap with the outcome. Based on exploratory factor analyses, the remaining 5 subscales loaded onto two summary scales, one measuring self-efficacy around HIV medication adherence, provider communication, and depression management, and the second measuring self-efficacy around HIV symptom management and social support. Both summary scales ranged from 1 to 10 and had high internal consistency (α = 0.93 and 0.88). Study arm was

not included as a potential confounder, since the mechanism by which change in depression might improve fatigue was hypothesized to result from interactions with a mental health professional and subsequent access to depression treatment and improved coping and self-efficacy skills, all of which were included in the analysis.

Analysis Sample

For inclusion in the present analysis, participants must have completed a baseline HAM-D within 14 days of enrollment, completed one or both of the 6- and 12-month interviews, and scored ≥8 on the baseline HAM-D (indicating depressive symptoms not in remission). Although all participants met criteria for current major depressive disorder on the MINI at the time of eligibility assessment, in some cases participants subsequently endorsed fewer depressive symptoms on the HAM-D during their baseline research interview.

Statistical Analysis

We used linear regression with generalized estimated equations to compare mean differences in fatigue severity between groups of depressive severity response, accounting for repeated measures on each individual. Depressive severity response was considered a categorical measure of full, partial or no response in depressive symptoms and as a continuous measure with a change of 1 unit corresponding to a 25 % improvement in depressive symptoms. We used locally weighted scatterplot smoothing (LOWESS) graphs to assess the assumption of linearity of the continuous measure of change in depression with the two measures of fatigue considered as outcomes. The distribution of fatigue scores was assessed to ensure it was approximately normally distributed using descriptive statistics (mean, median, skew and kurtosis). Additionally, we used logistic regression with generalized estimating equations to estimate the association between presence of any fatigue (yes or no) over time and continuously measured change in depressive severity. The association between presence of any fatigue and a categorical measure of depressive severity response was not assessed due to small cell sizes that led to lack of convergence. All final multivariable models were adjusted for all confounders, unless otherwise noted. The functional form of non-binary confounders (i.e., number of mental health contacts per quarter) with the outcome was assessed. Log transformations or polynomials were used to relax linearity assumptions when necessary. In a sensitivity analysis, we repeated all analyses with a modified HAM-D depressive severity score that omitted one item most closely related to the outcome (“How has your energy been in the past week? Have you felt tired?”). Statistical analyses were performed using Stata 13 (Stata-Corp, College Station, TX).

Results

Of 304 individuals enrolled in the trial, 242 had a baseline HAM-D within 14 days of enrollment and scored ≥8 on that HAM-D. Of those, 234 (97 %) completed a 6-month and/or a 12-month research interview (159 at 6 months and 127 at 12 months) and are included in this analysis.

Participants were on average nearly 44 years of age and predominantly male (70 %), black or African American (65 %), and unemployed (74 %). In addition to major depression, for

which all participants met criteria, nearly three-quarters of all participants (73 %) also met diagnostic criteria for an anxiety disorder, a substance use disorder, or both. On average, participants had approximately 2 mental healthcare contacts per quarter and had good clinical HIV indicators at baseline (mean CD4 count 607; 70 % with HIV RNA viral load <50 copies/mL) (Table 1). Demographic characteristics were similar across categories of highest depression response, with a few exceptions. There was a trend towards more mental health contacts per quarter and better depression response: those who never responded had 1.2 contacts, those who partially responded had 1.7 and those who responded had 2.1 contacts. A larger proportion of individuals who were not employed either partially responded (79 %) or responded (78 %), compared to those who did not respond (67 %).

At baseline, the mean fatigue intensity score was 6.9 on a 1–10 scale (Table 2). Nearly all individuals experienced either moderate (45 %) or severe (54 %) fatigue, with only 1 % reporting no fatigue (Table 2). The mean fatigue score decreased over time for the study population as a whole (mean of 5.4 at 6 months and 5.3 at 12 months). The proportion of participants experiencing severe fatigue decreased somewhat (33–35 % at 6 and 12 months). However, the proportion reporting moderate fatigue increased (54–59 %), and only a small minority reported no fatigue at follow-up (8–11 %).

Individuals who experienced stronger depression response (i.e., greater improvement in depression score) had larger decreases in fatigue. At 12 months, the mean fatigue score was 3.3 among those who demonstrated a full depression response, 5.5 among those who demonstrated a partial response, and 6.7 among those who demonstrated no response (Fig. 1). At 12 months, 29 % of those with a full depression response reported no fatigue compared to 3 % of those with a partial depression response and 2 % of those with no depression response (Table 2). Similar results were seen at 6 months. However, even among those who demonstrated a full depression response, nearly three-quarters continued to have either moderate or severe fatigue at 6 and 12 months.

In multivariable analyses of fatigue severity, compared to those with no depression response, partial depression response was associated with an average decrease of −0.52 points in fatigue severity on the 10-point scale (95 % CI −1.10, 0.06) and full depression response was associated with an average decrease of −2.01 points in fatigue severity (95 % CI −2.67, −1.41). Every 25 % improvement in depressive symptoms was associated with an average decrease of −0.40 points in fatigue severity (95 % CI −0.55, −0.26). When fatigue (yes or no) was considered as a binary outcome, a 25 % improvement in depression was associated with a 48 % reduction in the odds of any fatigue (OR 0.52, 95 % CI 0.32, 0.84) (Table 3).

In a sensitivity analysis using a modified HAM-D depressive severity total score that omitted one item asking about fatigue, all point estimates and conclusions about the inclusion of the null value in the 95 % confidence interval were substantively unchanged.

Discussion

In this sample of HIV-infected adults with depression participating in a depression treatment trial, we found a dose–response relationship between improvements in depression over the

course of the study and improvements in fatigue. Participants who demonstrated a full depression response over 12 months experienced greater improvements in fatigue than those demonstrating partial or no depression response, and each 25 % improvement in depressive severity was associated with a clinically meaningful improvement in fatigue. However, in most cases this improvement represented a shift from severe to moderate fatigue, with relatively few participants achieving fatigue remission even among those demonstrating a full depression response. Residual symptoms of depression such as fatigue are believed to predict a subsequently harder to treat course of depression [37, 38], and they are an indicator of a disorder which, in spite of improvement, is still present. This may call for vigorous and longer than usual continuation of antidepressant treatment, in order to prevent relapse. There is also good evidence for the use of cognitive therapy as an adjunct [38].

Overall, the study population mirrored the sociodemographics of the HIV epidemic in the Deep South, with a majority of participants being African American and male, and three out of four being unemployed. It is important to note that participants generally were clinically stable and relatively healthy with regard to their HIV infection. At baseline, nearly all participants were moderately or severely fatigued, an expected finding given that depression was a criterion for entry into the study.

There is some evidence that the multiple comorbidities of depression, such as fatigue, can be explained by neuroinflammatory, oxidative and nitrosative stress pathways [39]. Depression may be the clinical expression of peripheral cell-mediated activation, inflammation, and induction of oxidative and nitrosative stress pathways and of central microglial activation, decreased neurogenesis, and increased apoptosis. According to this model, these pathways underpin the pathophysiology of depression; the pathways detect illnesses such as HIV infection as threats and respond by signaling these threats as melancholy, anxiety, fatigue, and somatic symptoms. Depression contributes to increased neuroinflammatory burden and may therefore drive the inflammatory and degenerative progression [39]. This model would suggest that aggressive treatment of depression may help to decrease HIV-related fatigue. This hypothesis is partially supported by our data, as stronger depression response was associated with greater improvements in fatigue. However, a large proportion of participants in this study remained moderately or severely fatigued even after demonstrating a full depression response. These same pathways have been implicated in chronic fatigue syndrome and idiopathic fatigue [40], which may explain why treating depression will not fully resolve fatigue in HIV infection: chronic inflammation is key and must be addressed.

Few interventions have been developed to ameliorate HIV-related fatigue, but when implemented, they often improve depressive symptoms as well. Aerobic and resistance training was shown to decrease depression but not fatigue when compared to a sedentary group [17]. Rabkin et al. evaluated the efficacy and safety of armodafinil to treat HIV-related fatigue and assessed its effect on depressive symptoms. They found that armodafinil did not reduce depressive symptoms in the absence of improved energy. However, among participants with a depressive disorder at study entry whose energy improved, 82 % experienced improved mood as well [41]. Given the strong relationship between psychosocial factors and fatigue, Jong and colleagues [2] in a comprehensive review recommended research comparing the effect of medication (antidepressants, anxiolytics) and

behavioral interventions (cognitive-behavioral therapy, relaxation therapy, graded exercise therapy) to direct the best treatment strategy. The persistent coexistence of fatigue and depression [42] may need to be treated with psychosocial interventions in addition to medications.

One limitation of this study is the subjective nature of the measures of both the primary exposure (depressive severity) and outcome (fatigue). Both, however, were measured with well-validated scales by trained interviewers, and the HAM-D depressive severity measure is interviewer-scored rather than self-administered. A potential limitation is that the sample had relatively well-controlled HIV infection, so the results may not be generalizable to those who are more ill. Another limitation, in terms of generalizability, is that the study sample is restricted to individuals willing to enroll in a depression treatment trial. It is possible that individuals with more severe depression, and thus greater potential for response, chose to enroll in the study, which may have enhanced the relationship between change in depression and fatigue. A key strength of this study, in addition to its validated, longitudinal measures of depressive severity and fatigue, is the design as an additional analysis of a problematic symptom that may have been impacted by a depression treatment trial. Most prior studies of the relationship between depression and fatigue have been either cross-sectional or observational. The present analysis offers one of the first opportunities to explore the longitudinal impact of depression treatment on fatigue severity.

The findings reported here advance our understanding of the relationship between fatigue and depression among HIV-infected individuals and provide a new direction in terms of treatment of HIV-related fatigue. Aggressive treatment of depression may have the potential to improve fatigue in some HIV-infected individuals. The alleviation of both of these frequent conditions will mean an improved quality of life for those with HIV infection. A recent report found that stressful life events preceded depression and anxiety in a cohort of fatigued HIV-infected individuals who were followed for 3 years [18], so it may be that psychosocial interventions such as peer-assisted approaches, mindfulness-based stress reduction, and group approaches combined with aggressive psychopharmacological treatment may yield the most significant results. Jong et al.’s recommendation [2] to include behavioral interventions to treat HIV-related fatigue is sound, and those interventions likely will have the greatest impact if we can start with the aggressive treatment of depression, so our patients can participate fully in behavioral change. Although we may not yet fully understand the root cause of fatigue in HIV infection, there is hope that it is a modifiable condition.

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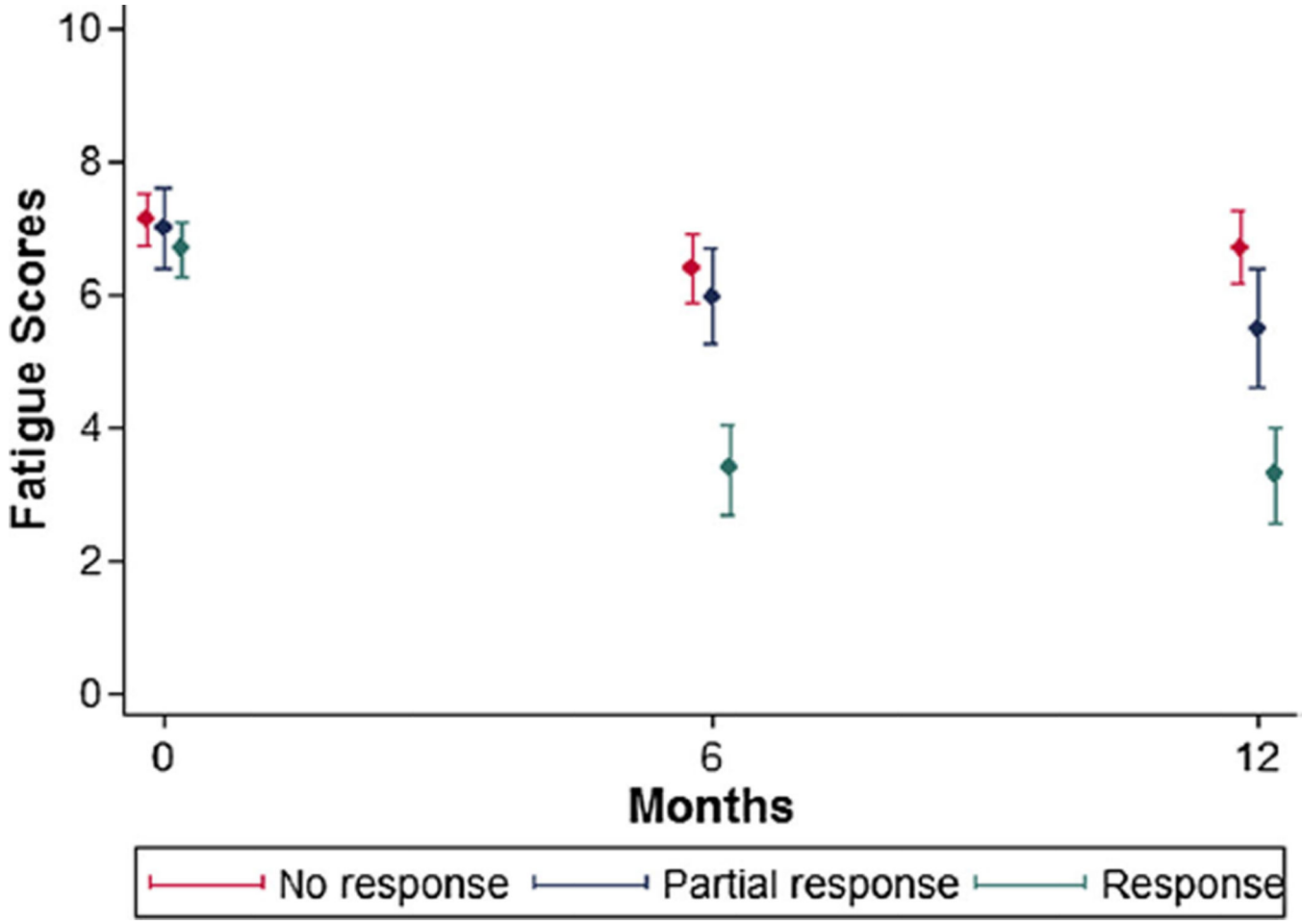

Fig. 1.

Fatigue intensity over 12 months, stratified by change in depressive symptoms from baseline. No/partial/full response: <25 %/ 25–49 %/>49 % improvement in depressive symptoms relative to baseline. The group categorized as “Response” at baseline includes all those who demonstrated full response at either 6 or 12 months. The group categorized “Partial response” at baseline includes all those who demonstrated partial response at either 6 or 12 months but never demonstrated full response. The group categorized as “No response” at baseline includes all those who never demonstrated partial or full response at either 6 or 12 months. At 6 and 12 months, participants are classified by their depression response status at that time point

Table 1

Baseline sociodemographic and clinical characteristics of 234 HIV-infected adults

Characteristic	N (%) or Mean (SD)
Age	43.5 (10.1)
Gender	
Male	164 (70.1)
Female	70 (29.9)
Race	
White or Caucasian	73 (31.2)
Black or African American	152 (65.0)
Other	9 (3.8)
Currently employed	
Yes	61 (26.2)
No	172 (73.8)
Psychiatric comorbidities	
Depression only	63 (26.9)
Comorbid anxiety	114 (48.7)
Comorbid substance abuse or dependence	18 (7.7)
Comorbid anxiety and substance abuse or dependence	39 (16.7)
Depressive severity (HAM-D) (range 0–52)	20.9 (6.1)
Adaptive coping (range 1:4)	2.7 (0.6)
Maladaptive coping (range 1:4)	2.1 (0.6)
Self-efficacy, scale 1 (range 1:10)[a]	5.5 (1.7)
Self-efficacy, scale 2 (range 1:10)[a]	9.3 (1.2)
Number of mental health contacts per quarter, over follow-up	1.8 (6.3)
CD4 count, cells/mm^3	607 (371.5)
HIV RNA viral load <50 c/mL	151 (69.6 %)

[a] *Scale 1* self efficacy around HIV medication adherence and provider communication. *Scale 2* self efficacy around depression management, HIV symptom management, and social support

Table 2

Fatigue severity and depression over time

	Overall	Change in depressive severity		
		No response	Partial response	Full response
Baseline (n = 234)				
Fatigue score, mean (SD)[a]	6.9 (1.9)	7.1 (1.8)	7.0 (2.0)	6.7 (2.0)
No fatigue, n (%)	3 (1.3)	1 (1.0)	0 (0.0)	2 (2.1)
Moderate fatigue (<7), n (%)	105 (45.3)	42 (43.8)	18 (42.9)	45 (47.9)
Severe fatigue (≥7), n (%)	124 (53.5)	53 (55.2)	24 (57.1)	47 (50.0)
6 months (n = 159)				
Fatigue score, mean (SD)[a]	5.4 (2.6)	6.4 (2.3)	6.0 (2.2)	3.4 (2.2)
No fatigue, n (%)	13 (8.3)	3 (3.9)	0 (0.0)	10 (22.7)
Moderate fatigue (<7), n (%)	92 (58.6)	39 (51.3)	23 (62.2)	30 (68.2)
Severe fatigue (≥7), n (%)	52 (33.1)	34 (44.7)	14 (37.8)	4 (9.1)
12 months (n = 127)				
Fatigue score, mean (SD)[a]	5.3 (2.7)	6.7 (2.1)	5.5 (2.4)	3.3 (2.4)
No fatigue, n (%)	14 (11.2)	1 (1.9)	1 (3.3)	12 (28.6)
Moderate fatigue (<7), n (%)	67 (53.6)	24 (45.3)	17 (56.7)	26 (61.9)
Severe fatigue (≥7), n (%)	44 (35.2)	28 (52.8)	12 (40.0)	4 (9.5)

[a] 2 people missing fatigue scores at all time points

Table 3

Adjusted association of improvement in depression with fatigue intensity over 12 months

Change in depressive severity	Fatigue severity (range 1–10)[a] Adjusted mean difference (95 % CI)	Any fatigue (yes/no)[b] Adjusted odds ratio (95 % CI)
Categorical		
No response	0.00 (ref)	n/a
Partial response	−0.52 (−1.10, 0.06)	n/a
Full response	−2.04 (−2.67, −1.41)	n/a
Continuous		
Per 25 % improvement in symptoms	−0.40 (−0.55, −0.26)	0.52 (0.32, 0.84)

NB: HIV medication adherence, provider communication and depression management self-efficacy were dropped from the model because high correlation with adaptive coping led to unstable standard errors

[a]Adjusted for: baseline age, adaptive coping, maladaptive coping, self-efficacy, number of mental health contacts per quarter and baseline psychiatric comorbidities

[b]Adjusted for: baseline age, adaptive coping, maladaptive coping, social support self-efficacy (only), number of mental health contacts per quarter and baseline psychiatric comorbidities