A biopsychosocial approach to HIV fatigue: A cross-sectional and prospective analysis to identify key modifiable factors

Dr Alicia M HUGHES[1], Dr Lucy CAMPBELL[1], Hannah GRAHAM[1], Professor Frank POST[2], Professor Trudie CHALDER[1],

[1] Department of Psychological Medicine, Institute of Psychiatry, King's College London, DeCrespigny Park, London, SE5 8AF

[2] Department of Sexual Health and HIV, King's College Hospital NHS Foundation Trust.

Corresponding author:

Professor Trudie Chalder, Trudie.Chalder@kcl.ac.uk

Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neurosciences

DeCrespigny Park

London, SE5 8AF

United Kingdom

Source of funding: National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

Abstract

This study aimed to identify the prevalence and predictors of current fatigue and fatigue at 1-year follow-up, in people with HIV. Participants were recruited from HIV outpatient clinics in London, England. We explored a range of bio-psychosocial factors associated with current fatigue severity, identifying the most salient factors in a multifactorial model. A prospective study explored the predictive value of specific psychological and behavioral factors in predicting fatigue severity at one year. Sixty-four of 131 (49%) participants met the criteria for clinically significant fatigue at baseline. Psychological and behavioral variables, but not immune-virologic markers or antiretroviral treatment, were associated with current fatigue severity. In the multifactorial model, catastrophizing and distress independently predicted current fatigue severity. Higher levels of fatigue at 1 year was predicted by baseline catastrophizing, symptom focusing, distress and sleep quality, when controlling for baseline fatigue, clinical and demographic variables. These findings suggest psychological and behavioral factors are important in the maintenance of fatigue in people with HIV and identify potential opportunities for treatment. Future interventions for fatigue in HIV should not only address anxiety, depression and distress but could be optimized by targeting psychological processes such as catastrophic thinking styles and symptom focusing.

Key Words

Anxiety, Depression, Fatigue, HIV, Illness Behavior,

Word count: 3,007

Introduction

One of the most prevalent and debilitating symptoms experienced by people living with HIV is fatigue. [1] The prevalence of fatigue in chronic HIV infection ranges from 33 to 88% [2] with a UK based study finding fatigue present in 65% of people with HIV. [3] Fatigue is associated with poorer quality of life and lower survival, [4] perhaps due to reduced adherence to anti-retroviral therapy (ART). [5] Importantly, laboratory markers of HIV disease progression, i.e. CD4 count and viral load, do not appear to be associated with fatigue. [2,4,6] Other disease and treatment related factors, such as duration of HIV infection, use ART as well as certain laboratory parameters (i.e. hemoglobin level, red blood count hematocrit and serum erythropoietin, hepatic enzymes, testosterone level) have been inconsistently associated with fatigue. [2,6-10] However, from a biopsychosocial perspective, disease and treatment related factors form only one part of the explanation. [11] Fatigue is multifactorial, influenced by a variety of biological, demographic, psychological, social and behavioral factors, which are poorly understood in HIV. The biopsychosocial perspective has been elaborated in cognitive behavioral models of fatigue, which propose that whilst disease and treatment related factors may trigger initial fatigue, cognitive and behavioral factors play a role in maintaining and perpetuating symptoms. [12,13]

Studies of fatigue in other long-term conditions have shown that cognitive and behavioral factors are important. [12] Across a number of chronic conditions negative illness representations, symptom interpretations and heightened symptom focusing have been associated with increased fatigue. [14-16] According to the cognitive behavioral model of fatigue, believing fatigue is serious, damaging, uncontrollable and incurable and thus must be monitored, can enhance symptom perception and amplify the severity of fatigue.

The literature also suggests that an individual's behavioral response to fatigue is important. Research has identified two different types of coping responses to fatigue; (i) avoidance and limiting behaviors; with associated beliefs that rest and reduced activity are helpful in controlling symptoms and (ii) all-or-nothing behaviors, whereby the individual pushes themselves to keep going until they 'crash'. [16-18] Avoidant coping styles have consistently been associated with increased fatigue in a number of long-term conditions. [19-23] Despite the clinical assertation that behavioral responses to fatigue are important there is relatively little literature exploring this aspect in relation to fatigue in long-term conditions.

Social support may also have a role to play. Social support is an important aspect of psychological adjustment for many people living with HIV infection and can buffer the stress associated with living with HIV. [24,25] A study of men with HIV in relationships, found that the quality and status of the relationship can influence the experience of distress, illustrating that one's primary relationship can serve both as a buffer and a source of distress. [26] There may also be a role for social support in relation to fatigue. A review with patients with chronic fatigue syndrome (CFS) found that patients experienced increased fatigue, disability, and distress when their significant other had solicitous and/or punishing responses. [27]

These psychosocial and behavioral factors remain relatively under-explored in HIV-related fatigue. A multifactorial model of HIV-related fatigue which identifies modifiable psychosocial and behavioral factors associated with and predictive of fatigue, could help provide more specific treatment targets.

The aims of this study were: to identify the prevalence of fatigue in this ethnically diverse HIV population; to cross-sectionally explore a range of bio-psychosocial factors

associated with fatigue severity; and to explore the predictive value of specific psychological and behavioral factors for levels of fatigue prospectively.

Methods

Sample

Between November 2011 and May 2013 consecutive participants attending HIV out-patients department in Kings College Hospital in London, England were approached to take part in a prospective cohort study. Individuals who were HIV-positive, 18 years of age or older, able to read and understand English were eligible. Patients were recruited irrespective of their treatment or current viral load status.

Procedure

Participants were accessed at the time of their routine medical appointments and provided with a participant information sheet. Informed consent was obtained prior to completion of the (paper) baseline questionnaire. Approximately 12 months later participants were sent a follow-up questionnaire by post to complete and return. The follow-up questionnaire was identical to the baseline questionnaire, with the exclusion of demographic questions. The study was approved by South East London Research Ethics Committee (10/H0808/135).

Measures

Demographics. Participants were asked to report standard demographic variables such as age, ethnicity, marital and occupational status, co-morbidities and HIV-related

variables such as risk factor for HIV infection, antiretroviral medications, and time since diagnosis.

Laboratory tests. After consent was provided laboratory test results were abstracted from electronic patient records, including the most recent viral load, CD4 count and nadir CD4 count.

Chalder Fatigue Questionnaire, CFQ. [28,29] A validated 11-item measure of physical and mental fatigue experienced over the preceding two weeks. Clinically significant fatigue was defined as a score >4 as per the authors instructions (21). The CFQ items were scored using the binary method (0 or 1) to establish the presence of clinically significant fatigue and a continuous method (0, 1, 2, 3) to assess fatigue severity. Cronbach's alpha in the current study was .93.

Cognitive Behavioral Responses Questionnaire, CBRQ. [16,30] A validated 40-item questionnaire assessing an individual's cognitive and behavioral responses to fatigue. Five subscales assess cognitive responses: catastrophic thinking, damage beliefs, symptom focusing, fearful beliefs about engaging in activity (fear avoidance) and embarrassment advoidance. Two subscales assess behavioral responses to symptoms: avoidance behavior and all-or-nothing behavior. Higher scores indicate more maladaptive responses to symptoms. Cronbach's alpha for the 7 CBRQ subscales were .85, .84, .91, .79, .82, .85, .92 respectively.

Hospital Anxiety and Depression Scale, HADS. [31] This 14 item scale measures levels of depression and anxiety, and has been shown to be a single factor model of distress [32].

Participants were asked to report how they had been feeling in the past week. Higher scores indicate greater levels of distress. Cronbach's alpha for HADS in the current study was .91.

Jenkins sleep questionnaire. [33] A 4-item scale which asks about trouble falling asleep, wake up times, having trouble staying asleep and unrefreshing sleep. Participants rated how frequently they had had these sleep problems; 'not at all', '1-3 days', '4-7 days', '8-14 days', '15-21 days', '22-31 days. The Cronbach's alpha for the Jenkins Sleep Questionnaire in the current study was .84.

Significant other social support, SOS. [34] Measuring perceived solicitous, distracting and punishing responses from a significant other. The social support measure was adapted from the West Haven-Yale multidimensional pain inventory to make it relevant to fatigue, without changing its meaning. Participants were asked to rate 14 statements to indicate how often their significant other generally responded to them in that particular way when they were experiencing symptoms of fatigue from 'never' to 'very often'. The Cronbach's alpha for the scales were .82, .78 and .78 respectively.

Data management and statistical analysis

Data were available on 131 participants and all variables had at least 75% completion; 24/131 participants did not complete the significant other social support scale (SOS). Where less than 25% of a variable was missing, except for demographic and clinical variables, multiple imputation was used (see supplementary materials). Statistical assumptions were verified using Kolmogorov-Smirnov tests and histograms to assess the distribution of the outcome variable fatigue. Assumptions of linear multiple regression, including normality of the residuals, linearity, homoscedasticity, no multicollinearity and

independence of residuals, were also assessed. For descriptive analyses, ANOVA and Kruskal-Wallis H tests were used to compare normally and non-normally distributed variables respectively.

To identify factors associated with fatigue severity at baseline, univariate analyses incorporating demographic, clinical and psychosocial variables were conducted. Variables significantly correlated at $p<.01$ level were entered into the multivariable models.

A hierarchical multiple linear regression analysis was conducted to determine the most important psychosocial and behavioral factors associated with fatigue at baseline, and whether these factors accounted for variance after the contribution of relevant demographic and illness-related factors. In step one, the control variables included in the model were clinical and demographic variables that significantly predicted fatigue at baseline. In the second step of the model, significant psychosocial variables were added. Variance inflation factors were examined for the potential for collinearity and over-fitting. [35]

Longitudinal analysis

Bivariate models were used to identify demographic, clinical, psychosocial and behavioral factors that were significantly associated with fatigue at 1-year follow-up. Variables significantly associated with fatigue at $p<.05$ level were included in the multivariable regression models. Separate linear regressions were conducted to explore whether psychosocial and behavioral variables continued to significantly predict fatigue at 1 year when controlling for baseline fatigue and significant clinical/demographic factors

Analyses were conducted using SPSS version 25.

Results

A total of 137 patients consented, of these 131 returned the completed the questionnaire. Participants were contacted 12 months later, and 66 (50%) completed the follow-up questionnaire. There were no significant differences in demographics or baseline fatigue scores among those who left the study and those who remained.

Characteristics of the population

Of the 131 people who completed the questionnaire 28% were female, with a mean age of 43.1 years (SD 9.8). Similarly to the demography of the overall clinic population, almost half were black-African/ black-Caribbean/black-British (45%). The majority of participants (89%) were on antiretrovirals (ARV's) with a median CD4 cell count of 491 cells/mm^3 and an undetectable viral load. Many had a history of severe immunodeficiency (median nadir CD4 counts 175 cells/mm^3). One third of participants were currently living with their partner, 62% were employed, 13% were on disability benefits/sick leave and 54% reported clinically significant fatigue (Table 1).

INSERT Table 1.

People with fatigue were more likely to be of white ethnicity, men who have sex with men (MSM), and diagnosed with HIV for longer. Being single was weakly associated with fatigue. Clinical and demographic parameters were not associated with fatigue.

Cross-sectional analysis

Table 2 shows cross-sectional correlations (Pearson's product moment correlation) between the psychological predictor variables and fatigue at baseline.

[INSERT Table 2]

Increased fatigue at baseline was associated with white ethnicity, $F(1, 122) = 37.23$; $p = .001$; $\eta_p^2 = .13$; MSM $F(1, 122) = 37.23$; $p = .001$; $\eta_p^2 = .13$, and more prolonged known HIV infection, $r(107) = 26$; $p = 01$. Significant correlations were observed across the psychological and behavioral variables with fatigue severity. Perceived social support was not associated with fatigue severity.

Table 3 shows the hierarchical linear regression model with baseline fatigue as the outcome variable. Step 1 entered demographic and clinical variables (risk: MSM vs. other; time since HIV diagnosis; and ethnicity). Step 2 added psychological and behavioral predictors (fear avoidance; catastrophizing; damage beliefs; symptom focusing; embarrassment avoidance; all-or-nothing behavior; avoidance resting behavior; distress; sleep quality).

[INSERT Table 3]

The first step of the model significantly predicted fatigue, explaining 9% of the variance in baseline fatigue. The only variable within Step 1 which significantly predicted fatigue was time since HIV diagnosis ($p = .04$), with those diagnosed for longer having increased fatigue severity. When psychological and behavioral factors were entered in the second step, the model explained an additional 46 % of the variance in baseline fatigue. Catastrophizing ($p = .04$) and distress were significant in Step 2 ($p = .001$).

Prospective study

At 1-year follow-up 52% (34/66) of the participants who responded met the cut-off for clinically significant fatigue; 8 (24%) were new cases of fatigue and 26 (76%) had

sustained fatigue. In 11 (30%) people, fatigue scores had reduced to below cut-off for clinically significant fatigue between baseline and follow-up.

The only significant associations between clinical and demographic variables and fatigue at follow-up were age (r=.34, *p*=.006) and risk factor (MSM v's other), *F*(1, 63) =10.19; *p*=.002; η_p^2 =.14, with MSM reporting more fatigue (mean= 16.98, SD=6.63) than others (mean=11.40, SD=7.37). Ethnicity was no longer significantly associated with fatigue and follow-up. Psychosocial and behavioral variables associated with fatigue at follow-up were explored using multiple linear regression (Table 4).

[INSERT Table 4]

Catastrophizing (*p*=.002), symptom focusing (*p*=.003), distress (*p*= .04) and sleep quality (*p*=.002) at baseline, remained significant independent predictors of fatigue severity at 1-year follow-up, when controlling for confounding.

Discussion

Over half of people with HIV included in this study met the criteria for clinically significant fatigue. Consistent with other studies there was no association between fatigue and laboratory markers of disease progression, treatment type (efavirenz versus other third agent) or treatment response. All analyzed psychological and behavioral variables were associated with current fatigue severity. In the multifactorial model, catastrophizing and distress independently predicted fatigue severity. Consistent with our hypotheses, fatigue severity at 1 year was significantly predicted by catastrophizing, symptom focusing, distress and sleep quality after controlling for clinical and demographic variables. These findings

provide further support for the biopsychosocial model of fatigue in HIV; highlighting the importance of psychological and behavioral factors in the maintenance of fatigue.

In terms of demographic factors, our findings support those in the literature, finding white ethnicity, MSM and older age was associated with increased fatigue severity. [10,36] [7,37,38] Longer time since diagnosis was associated with fatigue severity at baseline adding to the mixed findings in the HIV literature. [1,7-9,39,40]

All psychological and behavioral variables were associated with current fatigue severity. Consistent with other studies, distress was associated with an individual's current level of fatigue and predictive of fatigue severity at 1 year. [2,6,37] However, whilst distress predicted fatigue at 1 year the standardized co-efficient was lower than that for the other psychological and behavioral factors. Symptom focusing and catastrophizing were key predictors of current fatigue severity and fatigue at 1 year, even when controlling for distress and other confounding variables. Engaging in all-or-nothing behaviors was also associated with increased fatigue at baseline and follow-up, however it did not significantly predict fatigue severity once confounding factors such as baseline fatigue, age and risk of HIV transmission were entered into the models. This may be due to the high intercorrelation between self-report variables. It would be interesting to use more objective measures to assess behavioral responses to fatigue.

As with other studies, sleep quality was predictive of fatigue at 1 year follow-up [41]. Whilst fatigue and sleep quality were associated cross-sectionally, when entered into the multifactorial model, sleep quality was not significantly associated with fatigue severity. This may indicate that sleep disturbance is a function of other psychological processes. Indeed, sleep was significantly correlated with distress and all the psychological and behavioral

variables. In the HIV literature, sleep disturbances have consistently been associated with anxiety and depressive symptoms, as well as increased symptom burden and perceived stress. [42,43] The direction of these relationships is not clear, but it is likely to be reciprocal.

There were no associations between fatigue and social support in this sample. This is contrary to other HIV literature [44] and studies of fatigue in other long-term conditions. [27] It may be due to the measure used in this study tapping into the perceived type of support offered by a significant other, whereas other studies have focused on the amount of social support. [27,44,45] In addition there was some missing data for this scale (22/131 participants did not complete this question). It may be that those who had less social support and could not readily identify a significant other, did not complete this measure. These results should be interpreted with caution. More studies are needed to explore a wider range of different types of support that may be helpful for people with HIV who experience fatigue.

In intervention studies for other chronic conditions, changing cognitions, in particular fear avoidance beliefs and catastrophizing, have been found to mediate a reduction in fatigue [19,46-50]. This has been achieved through cognitive behavioral therapy (CBT) and graded exercise treatment protocols, developed specifically for fatigue. CBT interventions in HIV have focused on treating anxiety and depression [51]. Non-pharmacological interventions to specifically treat HIV related fatigue have included a 10-week stress-management intervention, relaxation techniques and exercise interventions [52-55]. Whilst these interventions show some promise, their evaluations have been limited by lack of validated fatigue measures and importantly none of these studies have explored the mechanisms of treatment. Developing treatment protocols to specifically target modifiable factors known to be associated with fatigue, could improve the efficacy of treatments. The

data from this study suggest that treatments for fatigue in HIV should not only target distress but should also challenge catastrophic thinking styles and symptom focusing, as well as incorporate sleep management protocols.

This study has several limitations. Half the sample was lost to follow-up, likely due to the length of the questionnaire. However, those that completed the follow-up were not statistically different to the sample at baseline. There were missing data for some variables, however all variables had a minimum of 75% completion, except for the significant other support scale, which was available for 82% of participants. There was overlap between measures; all CBRQ items were correlated. However, this measure has been validated in a recent factor analysis [30] and tolerance and variance inflation factor indicated multicollinearity was acceptable for the multifactorial model. We used a measure of distress which captures a combined score of anxiety and depression. Whilst it is widely used and, in this sample, had reliable internal consistency, other clinical diagnostic measures would provide further insights into the relationship between anxiety, depression and fatigue. The requirement for English in the study population was another limitation.

Conclusions

This and other studies illustrate that fatigue remains a common and debilitating symptom for people living with HIV. It seems that, whilst HIV and treatment related factors may trigger the initial fatigue, psychological and behavioral factors have a key role in fatigue maintenance for people living with HIV. This study has explored specific modifiable psychosocial and behavioral factors associated with and predictive of fatigue. In so doing it

has highlighted some key targets for interventions to help alleviate fatigue. Though there has been a call for national guidelines to manage fatigue in HIV [56] to our knowledge no studies have specifically developed treatment protocols to address fatigue in HIV. We would argue that a treatment model is needed for fatigue in HIV, which encompasses psychological, behavioral and sleep components. Interventions for fatigue in HIV should not only address anxiety, depression and distress but could be optimized by targeting psychological processes such as catastrophic thinking styles and symptom focusing.

Acknowledgements

The authors would like to thank Lawrence Matini for their assistance with data collection and Sheila Ali and Amani Krayem for their support with data entry and management.

Declaration of interest statement

Funding

AH and TC are part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, England. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Disclosures

TC is the author of self-help books for chronic fatigue. Authors disclose no other conflicts of interest.

References

1. Phillips KD, Sowell RL, Rojas M, Tavakoli A, Fulk LJ, Hand GA. Physiological and psychological correlates of fatigue in HIV disease. *Biological Research for Nursing.* 2004;6(1):59-74.
2. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. *Aids.* 2010;24(10):1387-1405.
3. Henderson M, Safa F, Easterbrook P, Hotopf M. Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy. *HIV Medicine.* 2005;6(5):347-352.
4. Barroso J, Voss JG. Fatigue in HIV and AIDS: an analysis of evidence. *Journal of the Association of Nurses in AIDS Care.* 2013;24(1):S5-S14.
5. Al-Dakkak I, Patel S, McCann E, Gadkari A, Prajapati G, Maiese EM. The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis. *AIDS care.* 2013;25(4):400-414.
6. Barroso J, Leserman J, Harmon JL, Hammill B, Pence BW. Fatigue in HIV-infected people: a three-year observational study. *Journal of pain and symptom management.* 2015;50(1):69-79.
7. Barroso J, Carlson JR, Meynell J. Physiological and psychological markers associated with HIV-related fatigue. *Clinical Nursing Research.* 2003;12(1):49-68.
8. Harmon JL, Barroso J, Pence BW, Leserman J, Salahuddin N. Demographic and illness-related variables associated with HIV-related fatigue. *Journal of the Association of Nurses in AIDS Care.* 2008;19(2):90-97.
9. Leserman J, Barroso J, Pence B, Salahuddin N, Harmon J. Trauma, stressful life events and depression predict HIV-related fatigue. *AIDS care.* 2008;20(10):1258-1265.
10. Voss JG. Predictors and correlates of fatigue in HIV/AIDS. *Journal of Pain and Symptom Management.* 2005;29(2):173-184.
11. Harvey SB, Wessely S. Chronic fatigue syndrome: identifying zebras amongst the horses. *BMC Medicine.* 2009;7(1):58.
12. Deary V, Chalder T, Sharpe M. The cognitive behavioral model of medically unexplained symptoms: A theoretical and empirical review. *Clinical Psychology Review.* 2007;27(7):781-797.
13. Vercoulen J, Swanink C, Galama J, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *Journal of psychosomatic research.* 1998;45(6):507-517.
14. Lukkahatai N, Saligan LN. Association of catastrophizing and fatigue: a systematic review. *Journal of Psychosomatic Research.* 2013;74(2):100-109.
15. Menting J, Tack CJ, Bleijenberg G, et al. Is fatigue a disease-specific or generic symptom in chronic medical conditions? *Health Psychology.* 2018;37(6):530.
16. Skerrett TN, Moss-Morris R. Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. *Journal of psychosomatic research.* 2006;61(5):587-593.
17. van der Werf SP, Prins JB, Vercoulen JH, van der Meer JW, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. *Journal of psychosomatic research.* 2000;49(5):373-379.
18. Ray C, Jefferies S, Weir WR. Coping with chronic fatigue syndrome: illness responses and their relationship with fatigue, functional impairment and emotional status. *Psychological medicine.* 1995;25(05):937-945.
19. Wiborg JF, Knoop H, Prins JB, Bleijenberg G. Does a decrease in avoidance behavior and focusing on fatigue mediate the effect of cognitive behavior therapy for chronic fatigue syndrome? *Journal of psychosomatic research.* 2011;70(4):306-310.

20. Nijs J, Roussel N, Van Oosterwijck J, et al. Fear of movement and avoidance behavior toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice. *Clinical rheumatology.* 2013;32(8):1121-1129.
21. Matcham F, Ali S, Hotopf M, Chalder T. Psychological correlates of fatigue in rheumatoid arthritis: a systematic review. *Clinical psychology review.* 2015;39:16-29.
22. Picariello F, Moss-Morris R, Macdougall IC, Chilcot J. The role of psychological factors in fatigue among end-stage kidney disease patients: a critical review. *Clinical kidney journal.* 2016;10(1):79-88.
23. Fukunishi I, Hayashi M, Matsumoto T, Negishi M, Hosaka T, Moriya H. Liaison psychiatry and HIV infection (I): Avoidance coping responses associated with depressive symptoms accompanying somatic complaints. *Psychiatry and clinical neurosciences.* 1997;51(1):1-4.
24. Earnshaw VA, Lang SM, Lippitt M, Jin H, Chaudoir SR. HIV Stigma and Physical Health Symptoms: Do Social Support, Adaptive Coping, and/or Identity Centrality Act as Resilience Resources? *AIDS and Behavior.* 2015;19(1):41-49.
25. Turner-Cobb JM, Gore-Felton C, Marouf F, et al. Coping, social support, and attachment style as psychosocial correlates of adjustment in men and women with HIV/AIDS. *Journal of behavioral medicine.* 2002;25(4):337-353.
26. Remien RH, Wagner G, Dolezal C, Carballo-Diéguez A. Levels and correlates of psychological distress in male couples of mixed HIV status. *AIDS care.* 2003;15(4):525-538.
27. Band R, Wearden A, Barrowclough C. Patient outcomes in association with significant other responses to chronic fatigue syndrome: A systematic review of the literature. *Clinical Psychology: Science and Practice.* 2015;22(1):29-46.
28. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. *Journal of psychosomatic research.* 1993;37(2):147-153.
29. Cella M, Chalder T. Measuring fatigue in clinical and community settings. *Journal of psychosomatic research.* 2010;69(1):17-22.
30. Ryan EG, Vitoratou S, Goldsmith KA, Chalder T. Psychometric properties and factor structure of a long and shortened version of the cognitive and behavioral responses questionnaire. *Psychosomatic medicine.* 2018;80(2):230-237.
31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica scandinavica.* 1983;67(6):361-370.
32. Norton S, Cosco T, Doyle F, Done J, Sacker A. The Hospital Anxiety and Depression Scale: a meta confirmatory factor analysis. *Journal of psychosomatic research.* 2013;74(1):74-81.
33. Jenkins CD, Stanton B-A, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. *Journal of clinical epidemiology.* 1988;41(4):313-321.
34. Kerns RD, Turk DC, Rudy TE. The west haven-yale multidimensional pain inventory (WHYMPI). *Pain.* 1985;23(4):345-356.
35. Kleinbaum DG, Kupper LL, Nizam A, Rosenberg ES. *Applied regression analysis and other multivariable methods.* Nelson Education; 2013.
36. Lee KA, Portillo CJ, Miramontes H. The fatigue experience for women with human immunodeficiency virus. *Journal of Obstetric, Gynecologic, & Neonatal Nursing.* 1999;28(2):193-200.
37. Barroso J, Hammill BG, Leserman J, Salahuddin N, Harmon JL, Pence BW. Physiological and psychosocial factors that predict HIV-related fatigue. *AIDS and Behavior.* 2010;14(6):1415-1427.
38. Sewell MC, Goggin KJ, Rabkin JG, Ferrando SJ, McElhiney MC, Evans S. Anxiety syndromes and symptoms among men with AIDS: a longitudinal controlled study. *Psychosomatics.* 2000;41(4):294-300.
39. Meynell J, Barroso J. Bioimpedance analysis and HIV-related fatigue. *Journal of the Association of Nurses in AIDS Care.* 2005;16(2):13-22.

40. Pence BW, Barroso J, Harmon JL, Leserman J, Salahuddin N, Hammill BG. Chronicity and remission of fatigue in patients with established HIV infection. *AIDS patient care and STDs.* 2009;23(4):239-244.
41. Lee KA, Gay C, Portillo CJ, et al. Symptom experience in HIV-infected adults: a function of demographic and clinical characteristics. *Journal of Pain and Symptom Management.* 2009;38(6):882-893.
42. Wu J, Wu H, Lu C, Guo L, Li P. Self-reported sleep disturbances in HIV-infected people: a meta-analysis of prevalence and moderators. *Sleep medicine.* 2015;16(8):901-907.
43. Rogers BG, Lee JS, Bainter SA, Bedoya CA, Pinkston M, Safren SA. A multilevel examination of sleep, depression, and quality of life in people living with HIV/AIDS. *Journal of health psychology.* 2018:1359105318765632.
44. Vosvick M, Gore-Felton C, Ashton E, et al. Sleep disturbances among HIV-positive adults: The role of pain, stress, and social support. *Journal of Psychosomatic Research.* 2004;57(5):459-463.
45. Honn VJ, Bornstein RA. Social support, neuropsychological performance, and depression in HIV infection. *Journal of the International Neuropsychological Society.* 2002;8(3):436-447.
46. Knoop H, Van Kessel K, Moss-Morris R. Which cognitions and behavior s mediate the positive effect of cognitive behavioral therapy on fatigue in patients with multiple sclerosis? *Psychological medicine.* 2012;42(1):205-213.
47. Wearden AJ, Emsley R. Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome. *Journal of consulting and clinical psychology.* 2013;81(5):831.
48. Stahl D, Rimes K, Chalder T. Mechanisms of change underlying the efficacy of cognitive behavior therapy for chronic fatigue syndrome in a specialist clinic: a mediation analysis. *Psychological medicine.* 2014;44(6):1331-1344.
49. Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *Journal of health psychology.* 2005;10(2):245-259.
50. Chalder T, Goldsmith KA, White PD, Sharpe M, Pickles AR. Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. *The Lancet Psychiatry.* 2015;2(2):141-152.
51. Spies G, Asmal L, Seedat S. Cognitive-behavioral interventions for mood and anxiety disorders in HIV: a systematic review. *Journal of affective disorders.* 2013;150(2):171-180.
52. Lechner SC, Antoni MH, Lydston D, et al. Cognitive–behavioral interventions improve quality of life in women with AIDS. *Journal of psychosomatic research.* 2003;54(3):253-261.
53. Fukunishi I, Hosaka T, Matsumoto T, Hayashi M, Negishi M, MORIYA H. Liaison psychiatry and HIV infection (II): application of relaxation in HIV positive patients. *Psychiatry and clinical neurosciences.* 1997;51(1):5-8.
54. O'Brien K, Nixon S, Tynan AM, Glazier R. Aerobic exercise interventions for adults living with HIV/AIDS. *Cochrane Database of Systematic Reviews.* 2010(8).
55. Webel AR, Perazzo J, Decker M, Horvat-Davey C, Sattar A, Voss J. Physical activity is associated with reduced fatigue in adults living with HIV/AIDS. *Journal of advanced nursing.* 2016;72(12):3104-3112.
56. Adinolfi A. The need for national guidelines to manage fatigue in HIV-positive patients. *Journal of the Association of Nurses in AIDS Care.* 2001;12:39-42.

Table 1. Demographic and clinic variables of the participants stratified by fatigue caseness

		Complete sample (n=131)	**Clinically significant fatigue present (CF<4) (n=64)**	**Clinically significant fatigue absent (CF 4-11) (n=67)**	**P-value**
Sex n (%)	Male	94 (71.7)	43 (67.2)	51 (76.1)	.33
Age (years) Mean (SD)		43(10)	42 (9)	44 (10)	.31
Ethnicity n (%)	Black	57 (45.2)	37 (59.7)	20 (31.3)	.01
*5 people declined to answer	White	60 (47.6)	22 (35.5)	38 (59.4)	
	Other	9 (7.1)	3 (4.8)	6 (9.4)	
Risk factor of HIV transmission n (%)	Heterosexual	49 (39.0)	31 (549.2)	18 (27.3)	.04
*2 people declined to answer	MSM	66 (51.2)	26 (41.3)	40 (60.6)	
	Other	14 (10.9)	6 (9.5)	8 (12.1)	
Viral load at questionnaire n (%)	Undetectable	102 (77.9)	50 (80.6)	52 (81.3)	.71
*missing data= 5	Not undetectable	14 (10.7)	8 (12.9)	6 (9.4)	
	Not on ARVs	10 (7.6)	4 (6.5)	6 (9.4)	
CD4 count at questionnaire (cells/m3): Mean rank [a]		517 (400)	509 (255)	524 (231)	.71
Nadir CD4 count (cells/m3): Mean rank [a]		265 (350)	184 (159)	217 (180)	.37
Time since HIV diagnosis (years): Mean rank [a] *missing data=24		10 (7)	8 (6)	12 (8)	.02
Currently on ART, n (%)		118 (90.1)	58 (90.6)	59 (89.1)	.60
	Efavirenz, n (%)	38 (32.2)	22 (37.9)	16 (27.1)	.90
Marital status, n (%)	Single	51 (44.7)	18 (34.6)	33 (58.9)	.13

*23 people declined to answer	Married/Living together	36 (31.6)	23 (44.2)	13 (23.2)	
	Divorced/separated	15 (13.2)	8 (15.4)	7 (12.5)	
	Widow (er)	2 (1.8)	1 (1.9	1 (1.8)	
	In a relationship but not living together	4 (3.5)	2 (3.9)	2 (3.6)	
Highest education attained, n (%)	None	4 (3.8)	2 (4.0)	2 (43.6)	.94
*26 people declined to answer	School	34 (32.4)	16 (32.0)	18 (32.7)	
	Vocational	10 (9.5)	6 (12.0)	4 (7.3)	
	Undergraduate	36 (34.3)	16 (32.0)	20 (36.4)	
	Postgraduate	21 (20.0)	10 (20.0)	11 (20.0)	
Employment status, n (%)*	Employed	68 (60.2)	36 (70.6)	32 (55.2)	0.56
*22 people declined to answer	Unemployed/looking for work	18 (15.9)	7 (13.7)	11 (19.0)	
	Student, not in paid employment	1 (0.9)	0 (0)	1 (1.7)	
	Homemaker, not working outside of home	2 (1.8)	0 (0)	2 (3.5)	
	Retired	3 (2.7)	1 (2.0)	2 (3.5)	
	Disability/sick leave	14 (12.4)	6 (11.8)	8 (13.8)	
	Other	3 (2.7)	1 (2.0)	2 (3.5)	

[a] Non-normally distributed variables were compared with Kruskal-Wallis H test. All other variables were normally distributed and compared with ANOVA's.

Table 2. Persons correlations matrix between fatigue and psychological, behavioral and social variables

	Fatigue at baseline (CFQ)	Fatigue at 1-year follow-up (CBRQ)	Fear avoidance (CBRQ)	Catastrophizing (CBRQ)	Damage beliefs (CBRQ)	Embarrassment avoidance (CBRQ)	Symptom focusing (CBRQ)	All-or-nothing behavior (CBRQ)	Avoidance rest behavior (CBRQ)	Distress (HADS)	Sleep quality (Jenkins)	Negative responses (SOS)	Solicitous responses (SOS)	Distracting responses (SOS)
Fatigue at baseline (CFQ)	1.0**	1.0**												
Fatigue at 1-year follow-up (CFQ)														
Fear avoidance (CBRQ)	.39**	.12	1.0**											
Catastrophizing (CBRQ)	.50**	.34*	.50**	1.0**										
Damage beliefs (CBRQ)	.31**	.12	.50**	.58**	1.0**									
Embarrassment avoidance (CBRQ)	.44**	.25*	.51**	.68**	.45**	1.0**								

Symptom focusing (CBRQ)	.43**	.29*	.46**	.82**	.56**	.76**	1.0**						
All-or-nothing behavior (CBRQ)	.45**	.33*	.28**	.39**	.30**	.37**	.44**	1.0**					
Avoidance rest behavior (CBRQ)	.50**	.22	.52**	.59**	.38**	.56**	.57**	.62**	1.0**				
Distress (HADS)	.66**	.40**	.38**	.65**	.38**	.60**	.66**	.50**	.60**	1.0**			
Sleep quality (Jenkins)	.52**	.56***	.31**	.38**	.16**	.27*	.37**	.46**	.50**	.58**	1.0**		
Negative responses (SOS)	.15	.22	.14	.12	.05	.18*	.17*	.30**	.25*	.20*	.15	1.0**	
Solicitous responses (SOS)	-.09	-.05	-.12	.06	.05	-.10	.09	.22*	.09	.02	-.08	-.06	1.0**
Distracting responses (SOS)	-011	-.08	-.08	.03	.08	-.13	.04	.19*	.01	-.004	-.05	-.03	.68	1.0**

*$p < .05$; **$p < .01$; ***$p < .001$; CBRQ, Cognitive Behavioral Responses Questionnaire; HADS, Hospital Anxiety and Depression Scale; Jenkins, Jenkins Sleep Scale; SOS, Support of Significant Other

Table 3. Multiple regression predictors of baseline fatigue (*n*=131)

Step & Variables	*B*	S.E. *B*	β
(1) Demographic and clinical variables			
Constant	12.09	1.42	
MSM vs other	.75	1.28	.06
Ethnicity	.85	.73	.13
Time since HIV diagnosis	.18	.09	.21*
R^2 = .09; *F* (3, 102) = 3.24; *p*=.03			
(2) Demographics, clinical, psychological and behavioral variables			
Constant	7.31	1.45	
MSM vs other	.67	1.0	.54
Ethnicity	.50	.54	.07
Illness duration	.04	.07	.04
Fear avoidance	.13	.12	.10
Catastrophizing	.42	.21	.28*
Embarrassment avoidance	.05	.11	.06
Symptom focusing	-.28	.15	-.27
All or nothing behavior	.09	.12	.07
Avoidance and rest	.02	.10	.03
Distress	.30	.09	.44***
Sleep	.15	.10	.15
ΔR^2 = .46; *F*(11, 102) = 10.35; *p*<.001			
Total R^2 = .56			

[1] Note: *B*= coefficient, S.E.*B* = standard error of coefficient, β= beta standardized β, * significant at the .05 level, ** significant at the .01 level, *** significant at the .001 level

Table 4. Multiple regression predictors of fatigue at 1-year follow-up with adjustment for clinical and demographic characteristics (*n*=66)

Step & Variables	*B*	S.E. *B*	β
Fatigue at 1-year follow-up			
Step 1			
Baseline fatigue	.24	.12	.24*
Age	.30	.07	.42***
MSM v's other	5.74	1.52	.39***
Step 2: Variables adjusted for fatigue, age, MSM			
Catastrophizing	.64	.20	.36**
Embarrassment avoidance	.19	.13	.17
Symptom focusing	.40	.13	.34**
All-or-nothing behavior	.30	.19	.19
Distress	.20	.10	.26*
Sleep quality	.48	.15	.37**

[1] Note: *B*= coefficient, S.E.*B* = standard error of coefficient, β= beta standardized β, * significant at the .05 level, ** significant at the .01 level, *** significant at the .001 level