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Fatigue in HIV-Infected People: A Three-Year Observational Study

Julie Barroso, PhD, **Jane Leserman, PhD**, **James L. Harmon, DNP**, **Bradley Hammill**, and **Brian W. Pence, PhD**

School of Nursing and Health Studies (J.B.), University of Miami, Coral Gables, Florida; Department of Psychiatry (J.L.), School of Medicine, and Gillings School of Global Public Health (B.W.P.), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and Duke University School of Nursing (J.L.H.), and Duke Clinical Research Institute (B.G.H.), Duke University School of Medicine, Durham, North Carolina, USA

Abstract

Context—HIV-related fatigue remains the most frequent complaint of seropositive patients.

Objectives—To describe the natural course of fatigue in HIV infection, in a sample (*n*=128) followed for a three-year period.

Methods—A longitudinal prospective design was used to determine what factors influenced changes in fatigue intensity and fatigue-related impairment of functioning in a community-dwelling sample of HIV-infected individuals. Participants were followed every six months for a three-year period. At each study visit, we collected data on a large number of physiological and psychosocial markers that have been shown to be related to fatigue in HIV-infected people. At three-month intervals between study visits, we collected data on fatigue via mailed questionnaires.

Results—Fatigue in HIV infection is largely a result of stressful life events, and is closely tied to the anxiety and depression that accompany such events. Fatigue did not remit spontaneously over the course of the study, indicating the need for interventions to ameliorate this debilitating symptom.

Conclusion—Intervening to help people who are suffering from HIV-related fatigue to deal with stressful life events may help to ameliorate this debilitating symptom.

Keywords

HIV; fatigue; physiological factors; psychosocial factors

Address correspondence to: Julie Barroso, PhD, University of Miami School of Nursing and Health Studies, P.O. Box 248153, Coral Gables, FL 33124-3850, USA, j.barroso1@miami.edu.

Disclosures

The authors declare no conflicts of interest.

Introduction

"Fatigue does not kill but it is common, disabling, and is regarded as a serious symptom by our patients, who may be victims of a variant of Tudor Hart's inverse care law – an inverse interest law - that the commoner a condition, the less the professional interest."[1]

Fatigue continues to be a troubling symptom for many with HIV infection,[2] with an estimated prevalence of 33-88%.[3] Research conducted in this area has been problematic: we have detailed in other papers a lack of consistent measurement; a lack of research focus on fatigue as a primary outcome of interest; a lack of longitudinal studies; and a failure to include multiple potential predictors of fatigue in data collection.[4-6] We have published several reports of our findings,[5,7-13] and there have been a number of other studies examining physiological and/or psychosocial factors related to fatigue in HIV infection; these are described below.

Since Jong et al. completed a comprehensive review of the literature in this area in 2010,[3] this review is focused on research conducted since that time. In their review, they found that the strongest predictors of fatigue among sociodemographic variables were unemployment and inadequate income. With regard to HIV-associated factors, combined antiretroviral therapy (ART) was the strongest predictor of fatigue. Interestingly, laboratory values were not predictive of fatigue. The strongest predictors were psychological factors such as depression and anxiety. They found that therapeutic interventions included testosterone, psychostimulants, dehydroepiandosterone (DHEA), fluoxetine, and cognitive behavioral or relaxation therapy.[3] These authors recommended the use of the HIV-Related Fatigue Scale, developed by the first author and used in the study reported herein.

Research published since the Jong et al. review[3] has extended our understanding of HIV-related fatigue. With regard to ART and illness-related variables, a recent meta-analysis found that fatigue still interferes with antiretroviral adherence;[14] however, fatigue was also among several factors that predicted virologic failure independent of adherence measures.[15] Fatigue was reported as the most frequent side effect of antiretroviral medications (71% of 953 participants), and was associated with worse health status, decreased work productivity, and/or increased health care resource use.[16]

Sleep disturbances in HIV-infected patients are understood now in greater detail, especially their relationship to psychological states. Lack of energy, which is closely related to fatigue, is associated with sleep disturbance, anxiety and depressive symptoms; lack of energy is more strongly related to morning fatigue than to evening fatigue.[17] Chinese women with HIV infection reported stress that was causing sleeplessness and fatigue.[18] Actigraphy revealed that the women did not have refreshing nocturnal sleep; they reported nightmares, worrying about disclosure of their diagnosis and transmission of the virus.[18] Insomnia severity scores were correlated with fatigue and anxiety symptoms in another study; sleep latency on two-week actigraphy was longer for HIV-infected participants, and sleep quality was reduced.[19] Trouble sleeping is associated with poor antiretroviral adherence.[20] HIV-infected participants who report difficulty falling asleep experience greater sleep disturbance and symptom burden, particularly anxiety and morning fatigue.[21] Greater insomnia severity

is associated with greater fatigue severity, and depression may contribute to both fatigue and insomnia.[22] High fatigue in both morning and evening is associated with anxiety, depression, and sleep disturbance.[23] Stress causes people living with HIV to become sleepless and fatigued; there were significant levels of sleep disturbance and fatigue, which were a result of the perceived stress of living with HIV infection.[24]

Of the psychosocial variables that have been correlated with fatigue, depression has been strongly and consistently related to fatigue in a number of studies. Anxiety, traumatic life events, post-traumatic stress disorder (PTSD), a lack of social support, and stressful life events also have been related to fatigue. Spirituality and religiosity predict increased religious coping, which influences social support, which in turn positively influences depression, which affects fatigue, and both depression and fatigue predict self-reported physical function.[25] Psychological factors such as depression, anger and fatigue contribute to the level of distress experienced with HIV-related symptoms.[26] Depression has long been associated with fatigue across illnesses, including HIV infection.[27] In the review by Jong and colleagues,[3] the strongest and most uniform associations were observed between fatigue and psychosocial factors such as depression and anxiety.

There is less evidence that physiological factors are associated with HIV-related fatigue, but there are some intriguing findings. The biological mechanisms are not well characterized. In an investigation of low-abundance plasma proteins in patients treated with nucleoside reverse transcriptase inhibitors (NRTIs) or those who were treatment naïve, the peptides apolipoprotein A-1, apolipoprotein B, histine-rich glycoprotein, alpha-1 B glycoprotein, and orosomucoid 2 were correlated with severity of fatigue; ApoA1 levels were higher in untreated patients, while ApoB results suggested a positive trend in treated patients.[28] A high fatigue pattern was associated with five single nucleotide polymorphisms in a study of plasma cytokines; this strengthens evidence for an association between fatigue and inflammation.[29] Fatigue was very common, despite viral suppression and good immune function; in a subgroup of patients, prior d-drug exposure and the presence of clinical lipodystrophy syndrome were associated with fatigue.[30] Fatigue severity was correlated strongly with symptomatic orthostatic intolerance. The literature on the relationship of fatigue to CD4 count and HIV viral load remains inconclusive; less fatigue was related to higher CD4 counts and lower HIV viral loads in a recent study.[31] Fatigued participants had lower levels of the cellular energy marker total creatine in the basal ganglia; this indicates energy dysmetabolism in this brain region, with striatal-cortical circuitry involvement.[27] Voss et al.[32] found fatigue-related gene networks in CD(14)+ cells; they identified 32 genes that were predictive of low versus high fatigue, along with mitochondrial inner membrane proteins. Neuropathic-related numbness preceded reports of fatigue, and muscle aches and numbness explained 28% of the random variance in the occurrence of fatigue.[33]

There have been few intervention studies. In a review of treatment strategies, Jong et al.[3] noted that studies on treatment strategies were minor in nature and focused on a select group of patients, most of whom had a major depressive disorder or clinical hypogonadism. Modafinil and armodafinil are the treatments with the most evidence; there have been multiple studies with robust sample sizes conducted by Rabkin and colleagues[34-39] and the results have consistently been reported as being effective in treating HIV-related fatigue.

Our work on nighttime sleep quality, daytime sleepiness, stressful life events, and HIV-related fatigue in this sample has been reported elsewhere.[10] We report here data on the following aim: to examine prospectively the relationships of personal and HIV-related variables and changes in physiological and psychosocial variables to fatigue intensity and fatigue-related impairment of functioning over time in HIV-infected individuals.

Methods

Sample

HIV-infected individuals 21 years of age or older who could read and speak English and were mentally competent to provide reliable data were considered eligible for the study. Mental competence and conditions that would preclude successful completion of the study were assessed during a detailed telephone screening interview by the principal investigator (PI). A total of 128 fatigued and non-fatigued persons were enrolled. Persons with a comorbid condition marked by fatigue were excluded, as were pregnant women and women less than 12 months postpartum. Flyers advertising the study were distributed at HIV/AIDS treatment centers and service organizations in North Carolina; these treatment centers are regional referral centers for patients from surrounding states. Although the word fatigue was prominent on the flyer, it stated that the study was open to both fatigued and non-fatigued people. The Institutional Review Board at Duke University Medical Center approved the study protocol, and study data were protected with a Certificate of Confidentiality from the National Institutes of Health. Written informed consent was obtained from each participant.

Procedures

Persons interested in participating in the study contacted the PI, who conducted the preliminary screenings by telephone. Participants were enrolled over a 14-month period. Potential participants were then contacted by one of the two study coordinators, and an initial visit was scheduled. The study visits were conducted at Duke's Clinical Research Unit. Participants were encouraged to take breaks whenever they became tired. They were paid $70 for each study visit. Study participants came in for a baseline visit and then every six months for three years, for a total of seven study visits. At each study visit, we collected data on a large number of physiological and psychosocial markers that have been shown to be related to fatigue in HIV-infected people. At three-month intervals between study visits, we collected data on fatigue via mailed questionnaires. All measures were performed at each visit, except when noted below, and all data were collected in face-to-face interviews and self-report questionnaires. The interviews and questionnaires were completed first, then blood was drawn for the physiological measures. Baseline demographic/medical data were collected at the first study visit by one of two research assistants. Patients were asked to rate their current health status at each study visit, and no participant reported receiving treatment for HIV-related fatigue during the study. We retained 78% of the participants for all seven data collection points. We allowed people to resume study visits if they missed a visit. There were no significant differences in fatigue scores among those who left the study and those who remained.

Physiological Measures

Physiological measures included hepatic function (AST, ALT, GGT, alk phos, T. bili, hepatitis C status), thyroid function (TSH, T4), HIV viral load, immunologic function (CD4, CD8, CD4/CD8 ratio, CD16, CD8CD38), gonadal function (testosterone, DHEA), hematologic function (hemoglobin, hematocrit, serum erythropoietin), and cellular injury (lactic acid). Thyroid and gonadal function were measured yearly because they are not subject to rapid change. Samples were transported and processed in the appropriate labs at Duke University Medical Center, using standard assay procedures. These labs are accredited by the College of American Pathologists and the Health Care Finance Administration.

Fatigue and Psychosocial Measures

Fatigue—The HIV-Related Fatigue Scale (HRFS)[4,5] is a Likert-type self-report measure with two scales measuring fatigue intensity (eight items, reported Cronbach's alpha 0.93) and impact of fatigue on daily functioning (22 items, reported Cronbach's alpha 0.98). A higher score on scales and items indicates more intense fatigue or greater adverse impact of fatigue; a mean score of ≥7 on the intensity scale indicates severe fatigue. Subjects whose intensity of fatigue is low (1 or 2) on all of the first seven HRFS items (i.e., my level of fatigue today; my level of fatigue on most days; how severe is the fatigue) are told to skip the rest of the instrument, because all of the remaining items are dependent on the subject being fatigued. Therefore, the few subjects with virtually no fatigue (n = 17) were given a "1" on all scales, subscales, and individual items.

Traumatic Events—Number of categories of traumatic events was adapted from previous research[40-43] and was assessed with a detailed interview. Childhood trauma was constructed by assigning one point for each of 14 traumas occurring at or before age 18. The number of categories of adult trauma included seven types of trauma occurring after age 18. Number of categories or types of traumatic events has been widely used in research; experiencing more types of trauma has been shown to predict higher rates of life-threatening medical conditions among health maintenance organization patients[40] and higher risk for mortality in HIV.[44] Because of our interest in predictors of fatigue, in this study we examined the number of categories of childhood and adult trauma separately.

Stressful Life Events—Recent stressful life events were measured via a methodology developed in a previous nine-year study showing that cumulative stressors predicted faster HIV disease progression.[45-47] Subjects completed a checklist of possible stressful life events and difficulties experienced during the previous six months (list originally modified from the Psychiatric Epidemiology Research Interview).[48] Subjects were then interviewed concerning the nature and context of each of the endorsed stresses. Interviewers objectively rated each stress from zero (no threat) to four (severe threat) using a manual of norms and vignettes, a methodology similar to that developed by Brown and Harris.[49] Norms for each stressful event were based on the degree of threat that most people would experience given the particular circumstances (e.g., financial impact, life threat, personal involvement). The objective threat rating was made independently from the subject's appraisal, in order to reduce the possibility that worsening disease or fatigue might lead to higher stressful event scores. The two research assistants were trained by one of the investigators (J.L.). They were

allowed to rate stresses independently, once they achieved reliability with the investigator's ratings (89–90% agreement, kappa = 0.83). Periodic reliability checks and retraining were done to insure that the interviewers maintained their consistency. All stresses rated above one were summed, except that we removed stressors that were likely to be caused by disease progression (e.g., CD4 count decline, retirement because of HIV worsening). We did not count stresses rated one, as these were typically positive stresses (e.g., job promotion) or daily hassles.

Depressive Symptoms—Depressive symptoms were measured with the Beck Depression Inventory-II (BDI-II), a 21-item instrument that assesses cognitive, affective and somatic symptoms of depression.[50] This widely used inventory has acceptable test-retest reliability (r = 0.79) in a nonclinical population. A score above 14 on the BDI-II is indicative of depression, with scores of 20–28 indicating moderate depression, and scores of 29 or above indicating severe depression. We omitted somatic symptom items that might overlap with HIV-related medical symptoms, thus changing the cut-off score for depression to 10.

Anxiety—The Hospital Anxiety and Depression Scale (HADS)[51] was used to measure anxiety. The HADS is a self-assessment mood scale, without somatic items, designed to identify non-organic anxiety and depressive states. Because the BDI-II and the HADS depression scales were highly correlated, we report only the anxiety findings from this scale. A score of 10 or higher on the anxiety subscale is diagnostic for that condition.[51] The anxiety subscale has a reported Cronbach's alpha of 0.89, showing strong internal consistency, and it correlates highly with the State Trait Anxiety Inventory (r = 0.68).[52]

Social Support—The Medical Outcomes Study Social Support Survey (MOS-SSS) contains 20 items that assess overall social support as well as five dimensions of support: emotional, informational, tangible, positive social interaction, and affectionate.[53] The scale uses a 1–5 Likert type rating scale (range, 20–100), with higher scores indicating greater support. Reported Cronbach's alphas are high for all of the subscales and for the total score (range, 0.91–0.97); one-year stability coefficients for the scales were also high (range, 0.72–0.79). In published reports, the instrument correlated strongly with other social support measures and was associated with a variety of mental and physical health outcome variables. Social support is measured yearly because it is a relatively stable variable.[53]

Post-Traumatic Stress Disorder (PTSD)—The Davidson Trauma Scale[54] was used to measure PTSD. It is a 17-item self-report measure, using a 5-point Likert rating scale, and it is based on the PTSD symptom clusters defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Scores range from 0 to 68 for each of the frequency and severity scales, and a score of 40 is diagnostic of PTSD. The total scale has demonstrated good test-retest reliability (r = 0.86) and internal consistency (r = 0.99). In diagnosing PTSD compared to the Structured Clinical Interview for DSM-IV Diagnoses (SCID), the positive predictive value was 92% and the negative predictive value was 79%.

Statistical Analysis

We used linear mixed-effects regression models to calculate unadjusted and adjusted effects of each physiologic and psychosocial measure on fatigue intensity and fatigue-related impairment of functioning. Each model allowed for an effect of time and included person-specific random intercepts. In these models, the level of each physiologic and psychosocial measure was broken down into two terms.[55] The first term, representing a between-person effect, contained each individual's mean value on a given variable averaged across all measured time points. In the mixed models, coefficients for these between-person terms reflect the association between an individual's average level of a given measure and that individual's average level of fatigue. The second term, representing a within-person effect, contained the person's deviation at each point in time from his or her overall mean on a given variable. In the mixed models, coefficients for these within-person terms reflect the association, for any individual, between changes in a given measure over time and contemporaneous change in fatigue. All physiologic and psychosocial variables were rescaled to have a standard deviation (SD) of 1.0 before modeling, such that reported coefficients represent the expected change in fatigue level, on a 1-10 scale, for a one SD change in the independent variable.

The ordering of predictor variables was determined empirically. We fit a series of nested models corresponding to our conceptual model of the relationships between sociodemographic, clinical, and psychosocial variables, and fatigue. Model 1a included sociodemographic variables that demonstrated statistically significant associations (at $P<0.05$) with either fatigue intensity or fatigue-related impairment of functioning, as well as three clinical indicators of *a priori* interest: CD4 count, HIV RNA viral load, and whether the participant was on ART. Model 1b included all variables from Model 1a as well as two additional laboratory values that demonstrated marginally significant bivariable associations with fatigue intensity: total testosterone and DHEA. Model 1c included all variables from Model 1b as well as lifetime exposure to traumatic experiences.

In Model 2, we introduced between- and within-person measures of exposure to recent stressful events and social support to test the hypothesis that these constructs would mediate any observed association between trauma and fatigue.[56-58]

In Models 3a-3c, we tested the hypothesis that current mental health symptomatology would mediate any association between recent stressful life events and fatigue.[59-61] In each model we introduced one of three measures of current mental health status: PTSD symptoms (Model 3a), anxiety symptoms (Model 3b), or depression symptoms (Model 3c). These measures were not included in a single model because of collinearity.

Results

Table 1 includes demographic data about the sample. We admitted fatigued (n=111) and non-fatigued (n=17) HIV-infected participants into the study. The majority of subjects were African American (66%), men (66%), unemployed (67%), and on ART (82%). The demographic distribution of the sample closely mirrors the HIV epidemiologic data for the state of North Carolina and the broader Southeast.[62] The median age was 44 years. The

median number of years of education was 12, and the median monthly income of the sample was $685. The sample predominantly comprised people who had lived with HIV infection for a long time, with a median of 10 years since diagnosis (range, 0-25 years). The mean CD4 count was 517/mm^3 (median 457), and 68% of the sample had HIV RNA viral loads <400 copies/mL.

Table 2 shows the unadjusted effects of sociodemographic and clinical characteristics with fatigue intensity and functioning over three years. Fatigue intensity and impairment of functioning tended to be higher among African Americans, among those with fewer years of education, and among those with lower incomes.

Tables 3 and 4 present unadjusted between- and within-person associations of psychosocial and physiological variables with the fatigue measures. Again, estimates for the between-person association reflect the effect of an individual participant's average over time, and the estimates for the within-person association reflect the effect of an individual participant's change over time. Childhood trauma was measured at the baseline visit only because it represents events that occurred in the distant past and does not change over time. For most psychosocial measures, both the between-person (mean) and within-person (deviation) effects were strong and significant increases in psychosocial distress were associated with increases in fatigue. On average, a one SD difference in mean depression score was associated with a 1.52 points higher score on the fatigue-related impairment of functioning scale (between-person effect; $P < 0.001$). Additionally, a within-person one SD change in their depression score was associated with a 0.66 point SD increase in fatigue-related impairment of functioning (within-person effect; $P < 0.001$). The largest effect sizes were observed for depression and anxiety, with a somewhat smaller effect size for PTSD and stressful life events. Effect sizes were generally comparable when modeling fatigue intensity (Table 3) compared to fatigue-related impairment of functioning (Table 4). Few physiological variables were related to fatigue intensity or fatigue-related impairment of functioning. Exceptions were between-person associations between testosterone, DHEA, and fatigue intensity; a between-person association between testosterone and fatigue-related impairment of functioning; and a within-person association between serum erythropoietin and fatigue-related impairment of functioning.

Table 5 presents the adjusted effects of clinical and psychosocial variables on fatigue intensity. After controlling for other factors, the between-person term for income was the only sociodemographic or clinical variable that remained significantly associated with fatigue (Model 1b). Each additional lifetime traumatic experience was associated with a 0.068-point higher fatigue score (Model 1c). Consistent with our mediation hypothesis, lifetime trauma had a nearly null association with fatigue intensity after including recent stressful events and social support in the model (Model 2).

In Model 2, each additional SD increase in recent stressful events was associated with a 0.43 point higher fatigue intensity score (between-person association). This association was partially attenuated but remained elevated and significant after adjustment for measures of current mental health (Models 3a-3c), consistent with a hypothesis that current mental health partially mediates the effect of stress on fatigue but that stress retains a direct effect on

fatigue independent of current mental health symptoms. The measures of mental health symptomatology were themselves strongly associated with fatigue intensity, with a one-SD increase in PTSD, anxiety, and depression symptoms corresponding to a 0.33, 0.53, and 0.48 point increase in fatigue intensity, respectively (between-person associations). The within-person associations were similar in direction and statistical significance to the between-person associations but smaller in magnitude.

Discussion

This study was designed to provide a prospective, longitudinal description of the natural course of fatigue in HIV-infected persons. Our sample of 128 people was typical of those with HIV infection in the southeastern U.S.: the majority of subjects were middle-aged, male, poor, unemployed African Americans. That most were African American somewhat limits the generalizability of our findings, but that is who is infected in the Deep South. We were interested in determining the chronicity of fatigue, and whether or not it would remit spontaneously over the course of the study. The participants who were the most fatigued at study entry were still the most fatigued at the end of data collection three years later. Also of note is that fatigue does not appear to remit spontaneously, which lends to the urgency to develop interventions for those who are most fatigued.

Over the three years of data collection, fatigue intensity and impairment of functioning tended to be higher among African Americans, among those with fewer years of education, and among those with lower incomes. People with fewer years of education tend to be in blue collar jobs that pay lower wages, and these jobs are often much more physically demanding than the white collar jobs available to those with more education. People with higher incomes often are able to hire people to do the most demanding activities, e.g., yard work, cleaning the house. We do not think that lower income affected access to care in our sample, as all reported having a primary care provider, and there was adequate clinical care for people with HIV infection, including those with limited funds or health insurance, in this particular geographical area.

Few physiological variables were related to fatigue intensity or fatigue-related impairment of functioning. After controlling for other factors, income was the only sociodemographic or clinical variable that remained significantly associated with fatigue. Each additional standard deviation increase in recent stressful events was associated with a 0.43 point higher fatigue intensity score. This association was partially attenuated but remained elevated and significant after adjustment for measures of current mental health (PTSD, anxiety and depression), consistent with our hypothesis that current mental health partially mediates the effect of stress on fatigue but that stress retains a direct effect on fatigue independent of current mental health symptoms. The measures of mental health symptomatology were themselves strongly associated with fatigue intensity, with a one SD increase in PTSD, anxiety, and depression symptoms corresponding to a 0.33, 0.53, and 0.48 point increase in fatigue intensity, respectively. Given the strong relationship between psychosocial factors and fatigue, Jong and colleagues[3] recommended research comparing the effects of medication (antidepressants, anxiolytics) and behavioral interventions (cognitive behavioral therapy, relaxation therapy, graded exercise therapy) to direct the best treatment strategy.

Several of our findings are striking; the longer a subject had been HIV-infected, the less fatigue they reported. It is possible that they have learned adaptive coping strategies that have helped them live with HIV as a chronic, manageable illness; it is also possible that they have modified their lives in incremental steps to accommodate fatigue. It is useful to know that physiological variables, including those that are disease markers for HIV infection, are not predictors of fatigue. Our findings suggest that monitoring lab values has little utility in identifying a cause for fatigue. It would still be appropriate to check for anemia and/or hypogonadism, but beyond that, there is no evidence that points to a physiological factor as a predictor of fatigue. Because of its unrelenting nature, it is critical that interventions be developed to lessen fatigue and its debilitating effects on HIV-infected individuals.

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Table 1

Description of sample

Characteristic	N (%) or Median (IQR)*
Demographic	
Age, years (range: 26-66)	44 (38-48)
Male gender	84 (65.6%)
Race:	
African American	84 (65.6%)
Caucasian	39 (30.5%)
Other	5 (3.9%)
Years of schooling (range: 4-20)	12 (12-14)
Employed part/full time	42 (32.8%)
Monthly income, $ (range: 0-6000)	685 (501-1300)
Clinical	
Years since HIV diagnosis (range: 0-25)	10 (6-15)
On any antiretroviral therapy	105 (82.0%)
CD4 count, cells/mm^3 (range: 29-1755)	457 (268-670)
HIV RNA viral load <400 copies/mL	87 (68.0%)
Fatigue course	
Fatigued at baseline	111 (88.1%)
Experienced remission of fatigue during follow-up**	11 (10.7%)

BLD: Below the limit of detection (400 copies/mL)

* IQR interquartile range (25th–75th percentile)

** Of 103 participants fatigued at baseline and with at least one follow-up visit.

Table 2

Bivariable predictors of fatigue intensity and impact on functioning over 3 years

	Intensity		Impact on functioning	
Predictor	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
Time since baseline, per 6 months	−0.01	(−0.02, 0.00)	−0.01	(−0.02, 0.00)
Mail-in (vs. in-person) assessment	0.44	(0.31, 0.56)	0.43	(0.30, 0.57)
Baseline fatigue intensity				
Baseline characteristics				
Male gender	−0.56	(−1.29, 0.16)	−0.41	(−1.16, 0.34)
African American race	0.70	(−0.01, 1.42)	0.91	(0.18, 1.65)
Education, per year	−0.20	(−0.33, −0.07)	−0.22	(−0.35, −0.08)
Time-varying sociodemographic characteristics				
Age, per 10 years	0.14	(−0.35, 0.63)	0.23	(−0.27, 0.74)
Income, per $\log_{10}$	−0.30	(−0.48, −0.13)	−0.25	(−0.43, −0.08)
Employed	−0.06	(−0.34, 0.21)	0.19	(−0.09, 0.47)
Time-varying clinical characteristics				
Years since HIV diagnosis, per year	−0.06	(−0.12, −0.01)	−0.07	(−0.13, −0.01)
On antiretroviral therapy	0.04	(−0.20, 0.29)	0.05	(−0.20, 0.31)
CD4, per 100 cells/mm^3	−0.05	(−0.12, 0.01)	−0.03	(−0.09, 0.04)
HIV RNA viral load, per $\log_{10}$	0.12	(−0.02, 0.25)	0.04	(−0.09, 0.18)
On antidepressants	0.06	(−0.24, 0.36)	0.18	(−0.13, 0.49)
Time-varying psychosocial characteristics				
Number of traumatic experiences	0.26	(0.09, 0.43)	0.22	(0.05, 0.40)
Number of stressful life events, past 6 months	0.12	(0.05, 0.20)	0.12	(0.04, 0.19)
Social support scale, per SD	−0.29	(−0.50, −0.08)	−0.22	(−0.44, 0.01)
PTSD scale, per SD	0.38	(0.24, 0.52)	0.44	(0.30, 0.58)
Beck depression scale, per SD	0.83	(0.68, 0.97)	0.88	(0.73, 1.02)
HADS anxiety scale, per SD				

Table 3

Between- and within-person associations of psychosocial and physiologic measures with fatigue intensity over 3 years

	Intensity					
	Between-person			Within-person		
Predictor	**Coefficient**	**95% CI**	**P value**	**Coefficient**	**95% CI**	**P value**
Psychosocial measures						
Number of stressful events	1.17	(0.69, 1.65)	0.000	0.14	(0.03, 0.24)	0.013
Davidson PTSD score	1.19	(0.82, 1.56)	0.000	0.27	(0.13, 0.42)	0.000
HADS anxiety score	1.63	(1.34, 1.91)	0.000	0.67	(0.52, 0.82)	0.000
Beck Depression Inventory score	1.52	(1.22, 1.82)	0.000	0.66	(0.50, 0.82)	0.000
Social support	−0.54	(−0.93, −0.15)	0.007	−0.11	(−0.29, 0.06)	0.213
Number of childhood traumas**	0.34	(0.14, 0.54)	0.001			
Number of adulthood traumas	0.26	(−0.07, 0.58)	0.125			
Number of all traumas	0.27	(0.10, 0.44)	0.002			
Physiologic measures						
Aspartate aminotranspertase	0.07	(−0.36, 0.50)	0.759	−0.02	(−0.18, 0.15)	0.835
Alanine aminotraspertase	−0.05	(−0.48, 0.37)	0.802	−0.06	(−0.23, 0.11)	0.478
Gamma glutamyl transpeptidase*	−0.03	(−0.41, 0.34)	0.866	0.01	(−0.26, 0.28)	0.925
Alkaline phosphatase	0.22	(−0.20, 0.63)	0.311	0.03	(−0.14, 0.20)	0.734
Total bilirubin	−0.10	(−0.57, 0.36)	0.661	0.00	(−0.14, 0.14)	0.978
TSH	−0.27	(−0.66, 0.11)	0.167	−0.13	(−0.31, 0.04)	0.138
Thyroxine	0.07	(−0.37, 0.51)	0.765	0.05	(−0.09, 0.19)	0.457
HIV RNA viral load*	0.31	(−0.14, 0.75)	0.176	0.10	(−0.04, 0.24)	0.156
CD4 count	−0.28	(−0.65, 0.08)	0.128	−0.12	(−0.39, 0.14)	0.370
CD4 percent	−0.33	(−0.69, 0.03)	0.073	−0.27	(−0.64, 0.10)	0.153
CD8	−0.36	(−0.75, 0.03)	0.072	−0.11	(−0.33, 0.11)	0.319
T4/T8 ratio*	−0.27	(−0.65, 0.11)	0.158	0.02	(−0.24, 0.28)	0.874
CD16 count	−0.28	(−0.73, 0.18)	0.238	0.02	(−0.12, 0.17)	0.743
CD16 percent	−0.14	(−0.61, 0.33)	0.561	0.04	(−0.10, 0.18)	0.591
CD38 on CD8	0.08	(−0.32, 0.49)	0.685	0.06	(−0.10, 0.23)	0.470
Total testosterone	−0.35	(−0.72, 0.01)	0.056	0.20	(−0.09, 0.49)	0.179
Free testosterone	−0.56	(−0.94, −0.18)	0.004	0.09	(−0.14, 0.33)	0.442
DHEA	−0.44	(−0.82, −0.06)	0.024	0.11	(−0.12, 0.35)	0.341
Hemoglobin	−0.21	(−0.57, 0.15)	0.254	−0.16	(−0.37, 0.05)	0.134
Hematocrit	−0.14	(−0.51, 0.24)	0.475	−0.14	(−0.34, 0.05)	0.143
Serum erythropoietin*	−0.27	(−0.68, 0.15)	0.209	0.10	(−0.11, 0.32)	0.347

	Intensity					
	Between-person			Within-person		
Predictor	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Lactic acid	−0.18	(−0.66, 0.31)	0.480	0.08	(−0.07, 0.23)	0.292

Table 4

Between- and within-person associations of psychosocial and physiologic measures with fatigue-related impact on functioning over 3 years

	Impact on functioning					
	Between-person			Within-person		
Predictor	**Coefficient**	**95% CI**	**P value**	**Coefficient**	**95% CI**	**P value**
Psychosocial measures						
Number of stressful events	1.15	(0.62, 1.67)	0.000	0.13	(0.02, 0.24)	0.022
Davidson PTSD score	1.31	(0.92, 1.70)	0.000	0.34	(0.19, 0.49)	0.000
HADS anxiety score	1.67	(1.34, 2.00)	0.000	0.68	(0.53, 0.84)	0.000
Beck Depression Inventory score	1.68	(1.36, 2.00)	0.000	0.70	(0.53, 0.86)	0.000
Social support	−0.65	(−1.07, −0.24)	0.002	−0.09	(−0.27, 0.09)	0.312
Number of childhood traumas**	0.29	(0.08, 0.51)	0.008			
Number of adulthood traumas	0.34	(−0.01, 0.69)	0.054			
Number of all traumas	0.26	(0.08, 0.44)	0.005			
Physiologic measures						
Aspartate aminotranspertase	−0.06	(−0.51, 0.40)	0.813	−0.03	(−0.20, 0.14)	0.746
Alanine aminotraspertase	−0.19	(−0.65, 0.27)	0.412	−0.09	(−0.26, 0.08)	0.294
Gamma glutamyl transpeptidase*	−0.08	(−0.49, 0.32)	0.678	−0.02	(−0.30, 0.26)	0.883
Alkaline phosphatase	0.16	(−0.29, 0.60)	0.492	0.06	(−0.11, 0.24)	0.469
Total bilirubin	0.04	(−0.46, 0.54)	0.869	0.08	(−0.07, 0.22)	0.293
TSH	−0.28	(−0.69, 0.14)	0.190	−0.09	(−0.27, 0.09)	0.324
Thyroxine	0.05	(−0.43, 0.52)	0.849	0.03	(−0.11, 0.18)	0.649
HIV RNA viral load*	0.33	(−0.14, 0.80)	0.171	0.02	(−0.13, 0.16)	0.803
CD4 count	−0.14	(−0.54, 0.25)	0.477	−0.07	(−0.35, 0.20)	0.603
CD4 percent	−0.23	(−0.62, 0.15)	0.239	−0.15	(−0.53, 0.23)	0.431
CD8	−0.36	(−0.77, 0.06)	0.093	−0.10	(−0.32, 0.12)	0.388
T4/T8 ratio*	−0.21	(−0.61, 0.19)	0.305	−0.09	(−0.35, 0.18)	0.523
CD16 count	−0.08	(−0.57, 0.41)	0.744	0.06	(−0.08, 0.21)	0.393
CD16 percent	0.02	(−0.48, 0.52)	0.928	0.05	(−0.09, 0.20)	0.449
CD38 on CD8	0.04	(−0.39, 0.48)	0.847	−0.04	(−0.21, 0.13)	0.673
Total testosterone	−0.30	(−0.69, 0.09)	0.133	0.10	(−0.20, 0.39)	0.523
Free testosterone	−0.43	(−0.84, −0.02)	0.042	0.03	(−0.21, 0.27)	0.787
DHEA	−0.38	(−0.79, 0.04)	0.074	0.04	(−0.19, 0.28)	0.715
Hemoglobin	−0.27	(−0.66, 0.12)	0.172	−0.16	(−0.37, 0.05)	0.145
Hematocrit	−0.24	(−0.64, 0.16)	0.239	−0.15	(−0.34, 0.05)	0.153

	Impact on functioning					
	Between-person			Within-person		
Predictor	**Coefficient**	**95% CI**	**P value**	**Coefficient**	**95% CI**	**P value**
Serum erythropoietin*	−0.11	(−0.56, 0.33)	0.619	0.24	(0.02, 0.46)	0.033
Lactic acid	−0.05	(−0.58, 0.48)	0.854	0.06	(−0.09, 0.21)	0.454

Table 5

Multivariable models of fatigue intensity and functioning over 3 years

	Presented as **Model 1**	*Coef (95% CI)* **Model 2**	**Model 3***
Time in study (per month)	−0.005 (−0.009, −0.000)	−0.005 (−0.009, −0.000)	−0.004 (−0.008, 0.000)
Psychosocial characteristics			
No. of types of traumatic experiences	0.068 (−0.002, 0.138)	−0.001 (−0.069, 0.068)	−0.022 (−0.087, 0.043)
Between-person differences:			
Number of recent stressful life events		0.431 (0.233, 0.629)	0.313 (0.118, 0.507)
Social support		−0.268 (−0.418, −0.118)	−0.220 (−0.362, −0.078)
PTSD symptoms			0.333 (0.173, 0.494)
Anxiety symptoms			0.527 (0.384, 0.669)
Depression symptoms			0.476 (0.309, 0.642)
Within-person changes:			
Number of recent stressful life events		0.081 (0.026, 0.136)	0.075 (0.020, 0.130)
Social support		−0.016 (−0.100, 0.068)	−0.012 (−0.096, 0.071)
PTSD symptoms			0.101 (0.028, 0.175)
Anxiety symptoms			0.263 (0.184, 0.343)
Depression symptoms			0.251 (0.169, 0.333)
Socio-demographic characteristics			
African American race	−0.052 (−0.370, 0.266)	−0.125 (−0.416, 0.166)	−0.163 (−0.435, 0.110)
Years of education	−0.011 (−0.074, 0.052)	−0.036 (−0.094, 0.022)	−0.035 (−0.089, 0.020)
Employed	−0.076 (−0.236, 0.084)	−0.108 (−0.265, 0.049)	−0.105 (−0.259, 0.049)
Income (between-person differences)	−0.146 (−0.232, −0.060)	−0.145 (−0.223, −0.066)	−0.142 (−0.215, −0.068)
Income (withn-person changes)	−0.035 (−0.072, 0.003)	−0.023 (−0.061, 0.015)	−0.020 (−0.057, 0.018)
Years since HIV diagnosis	−0.024 (−0.049, 0.000)	−0.013 (−0.036, 0.010)	−0.010 (−0.031, 0.012)
Physiologic characteristics			
On antiretroviral therapy	0.148 (−0.012, 0.307)	0.181 (0.023, 0.338)	0.171 (0.016, 0.326)
Between-person differences:			
CD4	−0.076 (−0.235, 0.082)	−0.108 (−0.253, 0.037)	−0.125 (−0.261, 0.011)
HIV RNA viral load (log10)	0.071 (−0.124, 0.265)	0.022 (−0.160, 0.204)	−0.026 (−0.198, 0.146)
Total testosterone	−0.023 (−0.199, 0.152)	−0.046 (−0.207, 0.115)	−0.037 (−0.188, 0.113)
DHEA	−0.125 (−0.293, 0.042)	−0.059 (−0.213, 0.095)	−0.027 (−0.172, 0.118)
Within-person changes:			
CD4	−0.009 (−0.146, 0.128)	−0.002 (−0.138, 0.134)	−0.003 (−0.138, 0.132)

	Presented as **Model 1**	*Coef (95% CI)* **Model 2**	**Model 3***
HIV RNA viral load (log10)	0.057 (−0.018, 0.133)	0.068 (−0.007, 0.143)	0.064 (−0.010, 0.139)
Total testosterone	0.045 (−0.080, 0.171)	0.053 (−0.071, 0.177)	0.063 (−0.060, 0.186)
DHEA	0.081 (−0.036, 0.199)	0.079 (−0.038, 0.195)	0.070 (−0.045, 0.186)

* Due to collinearity, three separate Model 3's were fit including one of the following: PTSD, anxiety, or depressive symptoms, along with all other covariates shown. Coefficients for all other covariates are from the model including PTSD symptoms and did not vary substantially between the three Model 3's.