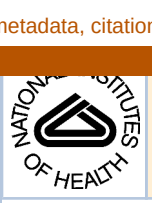

Published in final edited form as:

AIDS Behav. 2010 December ; 14(6): 1415–1427. doi:10.1007/s10461-010-9691-2.

Physiological and Psychosocial Factors that Predict HIV-Related Fatigue

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Abstract

Fatigue is one of the most common and debilitating symptoms experienced by HIV-infected people. We report the results of our longitudinal analysis of physiological and psychosocial factors that were thought to predict changes in HIV-related fatigue in 128 participants over a 1-year period, in an effort to sort out the complex interplay among a comprehensive set of physiological and psychosocial variables. Physiological measures included hepatic function (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, total bilirubin, hepatitis C status), thyroid function (thyroid stimulating hormone, thyroxine), HIV viral load, immunologic function (CD4, CD8, CD4/CD8 ratio, CD16, CD8CD38), gonadal function (testosterone, dehydroepiandrosterone), hematologic function (hemoglobin, hematocrit, serum erythropoietin), and cellular injury (lactic acid). Psychosocial measures included childhood and adult trauma, anxiety, depression, social support, stressful life events, and post-traumatic stress disorder (PTSD). Unemployment, not being on antiretroviral therapy, having fewer years since HIV diagnosis, more childhood trauma, more stressful life events, less social support, and more psychological distress (e.g., PTSD, anxiety and depression) put HIV-infected persons at risk for greater fatigue intensity and fatigue-related impairment in functioning during 1-year follow-up. Physiological variables did not predict greater fatigue. Stressful life events had both direct and indirect effects on fatigue.

Keywords

HIV; Fatigue; Stressful life events; Physiological factors; Psychosocial factors

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Introduction

While deaths from HIV infection have dropped dramatically, patients are still dealing with symptoms that interfere with their ability to lead full, productive lives. Fatigue is the most frequent and debilitating complaint of HIV-infected people, with estimated prevalence rates ranging from 55 to 65% [1–5]. The consequences of fatigue include having to stop working, limiting one's involvement with family and friends, and needing an entire day to get through the simplest of household chores. Fatigue is often chronic despite virologic suppression and immunological restoration; thus the cause is unclear.

Research to date has shown that a host of physiological and psychosocial factors may be correlated with fatigue in cross-sectional studies among people with HIV infection. Unfortunately, no studies have examined fatigue prospectively in order to determine whether physiological or psychosocial changes contribute to fatigue or its worsening. In addition to the lack of prospective data, no studies have examined an exhaustive list of physiological and psychological factors simultaneously and longitudinally. We discuss below each physiological variable that has been linked to HIV-related fatigue in previous research: those associated with hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glut-amyl transpeptidase [GGT], alkaline phosphatase [alk phos], total bilirubin [T. bili], hepatitis C status), thyroid function (thyroid stimulating hormone [TSH], thyroxine [T4]), gonadal function (testosterone, dehydroepiandrosterone [DHEA]), hematologic function (hemoglobin, hematocrit, serum erythropoietin), and cellular injury (lactic acid). We also examined the primary physiological variables that are affected by HIV disease progression: HIV viral load and immunologic function (CD4, CD8, CD4/CD8 ratio, CD16, CD8CD38). In addition, we discuss the psychosocial factors that may be associated with HIV-related fatigue: depression, anxiety, lack of social support, childhood and adult trauma, and stressful life events.

Research on Physiological Variables

Previous research on physiological variables and HIV-related fatigue has revealed conflicting findings. A lower CD4 count has been related to greater fatigue in some studies [6–8], but not in others [1,4,5,9–14]. Henderson et al. [4]. actually found greater fatigue in individuals with higher CD4 counts. Some studies found no relationship between fatigue and HIV viral load [5,9,12,15], whereas one found greater fatigue with a higher viral load [16].

In the general population, anemia is commonly associated with fatigue [17], as is low thyroid function (hypothyroidism) [18]. One study of HIV-infected persons found thyroid-stimulating hormone (TSH) was abnormally flattened over a 24-h period and did not show the variable 24-h rhythm of healthy individuals [19]. Barroso et al. [9]. found an inverse correlation between TSH and fatigue severity, which may reflect damage to the pituitary gland by the virus. Cytokines released in response to HIV infection could adversely influence thyroid homeostasis [20]. Low levels of testosterone [21] and low levels of dehydroepiandrosterone (DHEA) [22], common in people with HIV infection, may cause fatigue. Finally, some clinicians have observed fatigue with hepatic dysfunction [23,24]. There is a high prevalence of hepatitis C in seropositive people; those who are coinfected have been shown to have increased fatigue [25]. Other exploratory variables of interest, because of their possible relationships with fatigue, include CD16 cells, or natural killer cells, which are decreased in patients with stress and/or depressive symptoms [26]; CD8CD38 markers, which are markers of abnormal immune system activation [27,28]; and lactic acid, a non-specific measure of cellular injury and muscle breakdown [29].

Research on Psychosocial Variables

Psychosocial variables, particularly depression, have consistently been correlated with fatigue as well. The most common and persistent finding is the strong correlation of depressed mood with fatigue [1,4,5,9,30–33]. This is not surprising given that fatigue is part of the symptom complex of major depression and mood disturbance. Fatigue has also been associated with state and trait anxiety [9]. Indeed, some classification systems include fatigue among the criteria for a diagnosis of anxiety [34]. In one study [35], HIV-infected gay men reported more anxiety and stress than the general population, and anxiety and fatigue were related. Other psychosocial factors may also contribute to fatigue in seropositive individuals; for example, in one study [36], HIV-infected gay men who were less satisfied with their social support network were more likely to be fatigued. Stressful life events may also contribute to chronic fatigue [37]; such events have been associated with anxiety and depression in other populations [38–40]. Thus, stressful life events might contribute to fatigue directly or indirectly through their effects on anxiety and depression. Finally, a history of trauma is common among people with HIV infection, and with it comes a number of adverse psychological sequelae, including depression, anxiety, and post-traumatic stress disorder (PTSD) [41]. Therefore, measuring childhood and adult trauma is important to determine if they are contributors to fatigue in seropositive patients.

Baseline Data from this Study

We have previously reported baseline data from our longitudinal study examining predictors of HIV-related fatigue. We found more fatigue among those who were unemployed, had less monthly income, currently using antidepressants, and fewer years living with HIV infection [42]; however, none of the physiological variables we examined were significant [43]. The variables significantly related to HIV-related fatigue in our cross-sectional analyses of psychosocial variables included more childhood trauma, more recent stressful events, and more depressive symptoms; recent stresses were a more powerful predictor of fatigue than childhood trauma [37]. In this article we report the results of our longitudinal analysis of physiological and psychosocial factors as predictors of changes in HIV-related fatigue over time. The 1-year repeated measures design we are reporting was designed to sort out the complex interplay over time among a comprehensive set of physiological and psychosocial variables that have been found to be related to HIV-related fatigue, with the aim of identifying intervention points to ameliorate fatigue.

Methods

Sample

HIV-infected individuals 21 years of age or older who could read and speak English and were mentally competent enough to provide reliable data were considered eligible for the study. Mental competence and conditions that would preclude successful completion of the study, such as dementia or psychosis, were assessed during a detailed telephone screening interview by the PI, a doctorally prepared nurse practitioner. A total of 128 fatigued and non-fatigued persons were enrolled. Persons with a comorbid condition marked by fatigue, such as renal disease, cancer, or multiple sclerosis, 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 and see patients from surrounding states as well. 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 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, from March 2005 to May 2006. 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, which included reimbursement for transportation costs.

Study participants came in for a baseline visit and by the end of the study will have been followed every 6 months for 3 years, for a total of 7 study visits. This article includes data through visit 3, or 1 year of study participation. 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.

Retention was 86% (110/128) at 6 months and 88% (113/128) at 12 months. Of the 15 participants (12%) who did not complete the 12 month visit (visit 3), one had died, two had moved out of the area, three had requested to be withdrawn from the study, and nine could not be located. We allowed people to resume study visits if they missed a visit, which accounts for the increase in retention at 12 months when compared to 6 months. 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 since 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) [31] is a Likert-type self-report measure with two scales measuring fatigue intensity (8 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 7 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 ($n = 15$) are given a 1 on all scales, subscales, and individual items.

Traumatic Events: Number of categories of traumatic events was adapted from previous research [44–47] 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. These included: sexual abuse; physical abuse; growing up without enough to eat; primary caretakers with substance abuse, mental illness or suicidality; primary caretaker in prison; violence between primary caretakers; subject in foster care, orphanage or reform school; murder of close family members or friends; other deaths of immediate family members; death of a child; child with life threatening illness but not death; death of spouse or committed partner; and a life-

threatening illness or injury (not HIV). The number of categories of *adult trauma* included seven types of trauma occurring after age 18: sexual abuse, physical abuse, murder of close family members or friends, death of a child, child with life threatening illness but not death, death of spouse or committed partner, and a life-threatening illness or injury (not HIV). 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 [44] and higher risk for mortality in HIV [48]. 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 9-year study showing that cumulative stressors predicted faster HIV disease progression [49–51]. Subjects completed a checklist of possible stressful life events and difficulties experienced during the previous 6 months (list originally modified from the Psychiatric Epidemiology Research Interview) [52]. 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 [53]. 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 (JL). 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 maintain 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 due to HIV worsening). We did not count stresses rated one, as these were typically positive stresses or daily hassles (e.g. job promotion).

Depressive Symptoms: Depressive symptoms were measured with the Beck Depression Inventory II, a 21-item instrument that assesses cognitive, affective and somatic symptoms of depression [54]. This widely used inventory has acceptable test-retest reliability ($r = 0.79$) in a non-clinical 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) [55] 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. Since the BDI 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 [55]. The anxiety subscale has a reported Cronbach's alphas of 0.89, showing strong internal consistency, and it correlates highly with the State Trait Anxiety Inventory ($r = 0.68$) [56].

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 [57]. The scale uses a 1–5 Likert type rating scale (range 20–100), with higher scores indicate greater support. Reported Cronbach's alphas are high for all of the subscales and for the total score (range, 0.91–0.97); 1-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 since it is a relatively stable variable [57].

Post-Traumatic Stress (PTSD): The Davidson Trauma Scale [58] was used to measure post-traumatic stress disorder. 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 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%.

Data Analysis

We describe the baseline characteristics of the study participants using medians, quartiles, and ranges for continuous variables and percentages for categorical variables. We chose medians rather than means because of non-normal distributions of some continuous variables. For the repeated fatigue, physiologic, and psychosocial measures, we report means, standard deviations, and ranges for measurements pooled across all time points. We also describe the within-subject correlation in these measures using the intraclass correlation coefficient.

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 decomposed into two terms [59]. 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 terms (labeled "Mean") 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 terms (labeled "Deviation") reflect the association, for any individual, between changes in a given measure over time and contemporaneous change in fatigue. All fatigue, physiologic, and psychosocial variables were rescaled to have a standard deviation of 1.0 before modeling, such that reported coefficients represent the expected change in fatigue level, in standard deviations, for a 1 standard deviation change in the independent variable.

The ordering of predictor variables was determined empirically through previous analyses of this data set. The control variables included in each model were those that significantly predicted fatigue in our baseline analyses—employment status, monthly income (logged), antiretroviral therapy, years since HIV diagnosis—and those that were of particular interest—CD4 count and HIV RNA viral load. Model 1 contained the control variables listed above, that predicted fatigue in our baseline analysis, and early life trauma. Model 2 expanded Model 1 to include stressful life events and social support. Models 3–5 expanded Model 2 to include a measure of depression, anxiety, or PTSD symptoms. Because these three measures were highly correlated, we did not add them to the same model. We hypothesized that any association between fatigue and lifetime traumatic experiences or stressful life events would be mediated by current symptoms of depression, anxiety, and PTSD [60–62]. We tested this hypothesis with a series of nested models, examining the extent to which coefficients for trauma and stressful life events shifted with the addition of the hypothesized mediators to the model [63–65]. We assessed the potential for collinearity and over-fitting by examining variance inflation factors [66].

Results

The baseline sociodemographic and clinical characteristics of the study sample are described in Table 1. The majority of subjects were African American (66%), men (66%), unemployed (67%), and taking antiretroviral therapy (82%). The demographic distribution of the sample closely mirrors the HIV epidemiologic data for the state of North Carolina and the broader Southeast [67]. The median age was 44 years. The median number of years of education was 12, and the median monthly income of the sample was $686. The sample was predominantly made up of 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 the mean HIV viral load was 17,017 copies/ml (median viral load was 399) (mean log 10 viral load was 2.95; median log 10 viral load was 2.60). Many (n = 83, 65%) reported living with at least one other chronic illness (e.g., hypertension, depression, arthritis), and 25% had hepatitis C. Eighty-eight per cent of participants were fatigued at baseline, based on an in-depth interview with the PI. Those scoring ≥7 on the fatigue intensity subscale (indicating severe fatigue) ranged from 30 to 43% over the course of 12 months. A complete description of the sample can be found in Harmon et al. [42].

Table 2 provides the distribution and intraclass correlations of the fatigue measures, physiologic measures, and psychosocial measures over the three study visits. The mean score for fatigue intensity over three study visits was 5.7 (SD = 2.3); fatigue-related impairment of functioning was 4.9 (SD = 2.5). For each fatigue measure, the intra-class correlation was about 0.70, indicating higher variability among these scores between subjects than within subjects. That is, 70% of the total variability in fatigue scores was due to differences between individuals' mean fatigue levels, while the other 30% was due to changes in individuals' fatigue over time. Thus, there is some variability within subjects, even across the first 12 months of the study. Most of the psychological and physiological measures appear fairly consistent over time, in that subjects who score high at one time point tend to continue to score high at other time points. There is greater within subject variability on the Stressful Life Events measure, given that it reflects actual events that take place every 6 months.

Table 3 shows the unadjusted effects of each psychosocial variable and each physiological variable on the fatigue measures. Mean and deviation coefficients are reported for each scale (stressful life events, post-traumatic stress disorder, anxiety, depression, and social support). Again, estimates for the means reflect the effect of an individual participant's average over time, and the estimates for the deviations reflect the effect of an individual participant's change over time. Childhood trauma is measured at the baseline visit only since it represents events that occurred in the distant past, so it does not change over time. For most psychosocial measures, both the between-person (mean) and within-person (deviation) effects were strong and significant. On average, a 1 SD difference in mean depression score was associated with a 0.7 SD higher score on the fatigue-related impairment of functioning scale (between-person effect; $\beta = 0.713$, $P < 0.001$). Additionally, a within-person 1 SD change in their depression score was associated with a 0.2 SD increase in fatigue-related impairment of functioning (within-person effect; $\beta = 0.202$, $P < 0.001$). The largest effect sizes were observed for depression, anxiety, and PTSD, with a somewhat smaller effect size for stressful life events. Effect sizes were generally comparable when modeling fatigue intensity compared to fatigue-related impairment of functioning. With regard to the physiological variables, none of them were related to fatigue intensity or fatigue-related impairment of functioning with the exception of the mean effect of DHEA, which was related to fatigue intensity ($P = 0.045$). When fatigue was modeled as a dichotomous rather than continuous measure (fatigued vs. non-fatigued), unadjusted results were largely consistent, with fatigue being associated with more stressful events; greater PTSD, depression, and anxiety symptoms; and lower total and free testosterone levels (data not shown).

Table 4 presents the adjusted effects of psychosocial variables on fatigue intensity, and Table 5 presents the adjusted effects on fatigue related impairment of functioning. For both tables, model 1 includes demographic and illness-related variables, and number of childhood traumas; model 2 adds the number of stressful life events and baseline social support scores; model 3 adds the PTSD scores; model 4 adds the anxiety scores; and model 5 adds the depression scores. In the regression analysis, we kept the demographic, illness-related, physiological and psychosocial variables which were significant in previous analyses, or were of special interest, e.g., CD4 count and HIV viral load, and then brought in other key psychosocial variables. Since the two tables are so similar, we will limit the discussion of the findings primarily to fatigue intensity.

In model 1, more childhood trauma, being unemployed, not being on antiretroviral therapy, and fewer years since HIV diagnosis all significantly predicted greater fatigue intensity. History of traumatic experiences in childhood was associated with greater mean fatigue intensity (between-persons: $\beta = 0.121$, $P = 0.004$) and fatigue-related impairment of functioning (Table 5). In model 2, with the addition of stressful life events and baseline social support, the magnitude of the association between number of childhood traumas and fatigue was reduced; it was further reduced to nonsignificance in models 3–4 with the addition of PTSD and anxiety, and then is significant again with depression. Model 2 shows that stressful life events were associated with differences both between individuals and within individuals in fatigue intensity and fatigue-related impairment of functioning. Those participants who had a higher average number of stressful life events ($\beta = 0.308$, $P < 0.001$), and those who had a greater *increase* in the number of stressful life events ($\beta = 0.096$, $P = 0.023$), were more likely to have greater fatigue intensity over time. Results were nearly identical when predicting fatigue-related impairment of functioning.

The associations between stressful events and fatigue were somewhat attenuated by psychological variables (models 3–5); these associations either remained significant or were reduced to trends ($P \leq 0.10$). Thus part of the association between stressful events and fatigue appears to operate through psychological variables (indirect effect) but psychological variables do not mediate the entire effect: a direct effect appears to remain even after adjustment for psychological variables. Social support did not predict fatigue intensity, but did predict fatigue-related impairment of functioning ($\beta = -0.196$, $P = 0.004$); social support might play a role in mitigating the functional impairment associated with fatigue.

Models 3, 4 and 5 respectively show that PTSD, anxiety and depression were associated with differences between individuals on fatigue intensity and fatigue-related impairment of functioning; anxiety and depression were associated with differences within individuals on both fatigue measures. Specifically, those who had higher average PTSD ($\beta = 0.307$, $P < 0.001$), anxiety ($\beta = 0.568$, $P < 0.001$), and depression ($\beta = 0.535$, $P < 0.001$) and those who had a greater increases in anxiety ($\beta = 0.242$, $P < 0.001$) and depression ($\beta = 0.212$, $P < 0.001$) were more likely to have greater fatigue intensity over time. Variance inflation factors for all covariates were low (1.1–1.6).

Discussion

This study showed that being unemployed, not being on antiretroviral therapy, having fewer years since HIV diagnosis, more childhood trauma, more stressful life events, less social support, and more psychological distress (e.g., PTSD, anxiety and depression) put HIV-infected persons at risk for greater fatigue intensity and fatigue-related impairment in functioning during 1-year follow-up. Physiological variables (e.g., CD4, viral load, thyroid functioning) did not predict greater fatigue. Stressful life events had both direct and indirect effects on fatigue.

Limitations of the study should be acknowledged. The self-referral method of recruitment in this study may have introduced selection bias, as individuals experiencing fatigue may have been more likely to respond to study advertisements than those not fatigued; hence, the proportion of fatigued participants in this study may be an overestimate of the prevalence of fatigue among HIV-infected individuals generally. Self-reported measures of fatigue may be subject to misclassification which, if non-differential by other covariates, would tend to bias estimates of association toward the null. There is also a risk of inflated Type I error due to the number of statistical tests performed in this study. As is common in observational research, no formal correction was made for multiple comparisons [68]. However, the statistical significance of the associations of greatest interest—e.g., those due to changes in psychosocial factors reported in Tables 4 and 5—and the substantive conclusions of this paper would remain unchanged if a Bonferoni-adjusted *P* value threshold of 0.05/30 = 0.0017 were applied.

Despite these limitations, this study provides us with useful information that should help us in developing interventions to ameliorate fatigue. We started this study examining a very large number of personal, illness-related, physiological, and psychosocial factors that have been shown in different studies to be related to HIV-related fatigue. Ours is the first study to examine all of these factors simultaneously and longitudinally, and to use a fatigue measure that was developed specifically for HIV-infected individuals.

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.

We were surprised at both the number and strength of the psychosocial predictors of fatigue. While baseline social support was not a predictor of fatigue intensity, it was a predictor of fatigue-related impairment of functioning. It is possible that those participants with more social support had people who could assist with tasks such as activities of daily living. Post-traumatic stress disorder, anxiety, and depression—all current mood states—were generally strong predictors of increases in fatigue intensity and in fatigue-related impairment of functioning. For the most part, these relationships were true both between individuals and within individuals, indicating that higher average scores or increases in the scores of these current mood states predicted increases in fatigue intensity and in fatigue-related impairment of functioning. A somewhat smaller effect size was seen for stressful life events. We hypothesized that any association between fatigue and lifetime traumatic experiences or stressful life events would be mediated by current symptoms of depression, anxiety, and PTSD [60–62]. This was partially true; depression and anxiety were mediators of childhood trauma and stressful life events. In terms of developing a model to predict fatigue, we should note that both childhood trauma and an increase in stressful life events precede the worsening of fatigue; the stressful life events interview concerns events during the previous 6 months. It appears that participants with childhood trauma and those with more stressful events have more psychological distress and more chaotic lives and thus more fatigue. In severe cases, the traumatic events lead to post-traumatic stress disorder, which leads to fatigue.

While we look forward to analyzing the rest of our data, these findings provide a direction for the development of an intervention to ameliorate fatigue. While depression and anxiety are very closely related, they are in fact two different mood states, and are preceded by stressful life events or trauma. We believe that cognitive behavioral therapy may be effective in helping

our participants learn how to better deal with stress. In other analyses of our data, we have also found that fatigue is chronic and unremitting, and that those who came into the study the most fatigued have remained the most fatigued [69], making the need for an intervention even more critical. With HIV-infected people living longer than ever due to effective antiretroviral therapies, we must continue to try to find ways to lessen the fatigue that plagues so many of them.

Acknowledgments

The study featured here, entitled Fatigue in HIV-Positive People, is funded by the National Institute of Nursing Research, National Institutes of Health (NIH), 5R01NR008681, Sept. 1, 2004–May 31, 2009 (Julie Barroso, principal investigator), and grant number 1UL1RR024128-01, National Center for Research Resources, Duke CTSI, NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR, NINR, or NIH.

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Table 1

Demographic and clinical characteristics of sample at baseline (n = 128)

Characteristic	*N* (%) or median (IQR)[a]
Age, years (range: 26–66)	44 (38–48)
Female	44 (34.4%)
Race	
African-American	84 (65.6%)
Caucasian	39 (30.5%)
Other	5 (3.9%)
HIV risk factor	
MSM[b]	50 (39.1%)
Heterosexual sex	42 (32.8%)
IDU[c]	12 (9.4%)
Other/multiple/don't know	24 (18.8%)
Years of schooling (range: 4–20)	12 (12–14)
Monthly income (range: $0–$6,000)	$686 ($504–$1,300)
Employed part/full time	42 (32.8%)
Years since HIV diagnosis (range: 0–25)	10 (6–15)
On any antiretroviral therapy	105 (82.0%)
Currently using street drugs	28 (21.9%)
Current alcohol problem	12 (9.4%)

[a] *IQR* interquartile range (25th–75th percentile)

[b] *MSM* men who have sex with men

[c] *IDU* injection drug use

Table 2

Distribution and intraclass correlations of HIV-related fatigue measures, physiologic measures, and psychosocial measures over 3 study visits

Measure	Number of measurements	Mean (SD)	Study range/standard range	Intraclass correlation
HIV-related fatigue measures				
Fatigue intensity	347	5.7 (2.3)	1.3–9.8	0.70
Fatigue-related impairment of functioning	347	4.9 (2.5)	1.1–10.0	0.71
Psychosocial measures				
Number of stressful events	350	1.4 (1.5)	0.0–8.0	0.25
Davidson PTSD score	349	38.4 (34.9)	0.0–135.0	0.53
HADS anxiety score	350	16.3 (4.4)	7.0–27.0	0.62
Beck Depression Inventory score	350	13.1 (9.4)	0.0–42.0	0.64
Social support	240[a]	3.7 (1.0)	1.1–5.0	0.63
Number of childhood traumas	127[b]	2.0 (1.7)	0.0–8.0	–
Physiologic measures				
Hepatic function				
Alkaline phosphatase (alk phos)	344	100.9 (41.2)	48.0–373.0	0.80
			30–135	
Total bilirubin (T. bili)	344	0.7 (0.7)	0.1–5.4	0.62
			0.2–1.2	
Aspartate aminotranspertase (AST)				
Among HCV-uninfected	258	31.6 (14.7)	11.0–150.0	0.22
Among HCV-infected	84	66.6 (32.3)	18.0–150.0	0.80
			10–60	
Alanine aminotraspertase (ALT)				
Among HCV-uninfected	258	31.6 (14.7)	11.0–150.0	0.22
Among HCV-infected	84	65.1 (37.4)	15.0–150.0	0.83
			10–60	
Gamma glutamyl transpeptidase (GGT)				
Among HCV-uninfected	257	56.6 (62.3)	4.0–567.0	0.74
Among HCV-infected	86	154.2 (143.7)	16.0–613.0	0.88
			8–55	
Thyroid function				
TSH	237[a]	1.5 (0.9)	0.3–6.0	0.63
			0.34–5.66	
Thyroxine	236[a]	0.7 (0.1)	0.4–1.2	0.50
			0.52–1.21	
HIV RNA viral load	348	17788.3 (77834.2)	49.0–750001	0.82
			non-detect.	
Immunologic function				

Measure	Number of measurements	Mean (SD)	Study range/standard range	Intraclass correlation
CD4 count	349	529.8 (349.9)	6.0–1755.0	0.88
			400–1400	
CD4 percent	349	24.9 (11.9)	2.0–59.0	0.93
			31–61	
CD8 count	345	1031.5 (531.5)	62.0–3000.0	0.80
			250–1000	
CD4/CD8 ratio	345	0.7 (1.6)	0.0–28.0	0.09
			0.85–4.10	
CD16 count	343	117.8 (125.2)	0.0–600.0	0.20
			50–400	
CD16 percent	343	5.7 (5.1)	0.0–27.0	0.11
			0–1.0%	
CD38 on CD8	344	65.1 (16.0)	17.0–97.0	0.69
			Nml ranges not established	
Gonadal function				
Total testosterone	236[a]	388.7 (321.1)	6.0–1300.0	0.87
			240–950	
Free testosterone	232[a]	9.1 (7.6)	0.1–30.0	0.76
			9–30	
DHEA	237[a]	114.4 (84.9)	14.0–421.0	0.79
			35–430	
Hematologic function				
Hemoglobin	348	14.3 (1.7)	8.0–19.0	0.78
			12–15.5	
Hematocrit	348	0.4 (0.0)	0.2–0.6	0.74
			0.35–0.45	
Serum epo	233[a]	18.7 (39.0)	2.9–503.0	0.78
			4–21	
Cellular injury				
Lactic acid	348	1.5 (0.7)	0.5–4.9	0.33
			0.5–2.2	

[a] Only measured at baseline and 12-month visits

[b] Only measured at baseline

Table 3

Unadjusted effects of psychosocial and physiologic variables on fatigue intensity and fatigue-related impairment of functioning

Measure	Fatigue intensity				Fatigue-related impairment of functioning			
	Effect of within-person …				Effect of within-person…			
	Mean		Deviation		Mean		Deviation	
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
Psychosocial measures								
Number of stressful events	0.439	< 0.001	0.097	0.021	0.414	< 0.001	0.090	0.032
Davidson PTSD score	0.540	< 0.001	0.077	0.156	0.559	< 0.001	0.082	0.124
HADS anxiety score	0.726	< 0.001	0.220	< 0.001	0.688	< 0.001	0.227	< 0.001
Beck Depression Inventory score	0.689	< 0.001	0.222	< 0.001	0.713	< 0.001	0.202	< 0.001
Social support	−0.206	0.018	−0.120	0.163	−0.278	0.001	0.003	0.969
Number of childhood traumas[a]	0.251	0.001	–	–	0.280	< 0.001	–	–
Physiologic measures								
Aspartate aminotranspertase	0.027	0.770	−0.105	0.122	−0.001	0.992	−0.076	0.250
Alanine aminotraspertase	−0.038	0.677	−0.102	0.130	−0.071	0.440	−0.107	0.101
Gamma glutamyl transpeptidase[b]	0.008	0.926	−0.189	0.099	0.005	0.954	−0.129	0.258
Alkaline phosphatase	0.136	0.119	−0.130	0.133	0.142	0.105	−0.087	0.303
Total bilirubin	−0.046	0.621	0.005	0.934	−0.005	0.956	0.042	0.465
TSH	−0.042	0.634	−0.153	0.076	−0.032	0.721	−0.008	0.924
Thyroxine	0.003	0.975	0.105	0.173	0.037	0.684	0.083	0.265
HIV RNA viral load[b]	0.093	0.342	0.013	0.803	0.058	0.551	−0.035	0.506
CD4 count	−0.130	0.124	−0.100	0.339	−0.070	0.411	0.023	0.827
CD4 percent	−0.150	0.068	−0.140	0.342	−0.108	0.192	−0.033	0.823
CD4/CD8 ratio	−0.151	0.085	−0.116	0.173	−0.122	0.168	−0.020	0.817
T4/T8 ratio[b]	−0.125	0.151	0.064	0.477	−0.094	0.279	−0.030	0.736
CD16 count	−0.130	0.266	0.018	0.699	−0.020	0.866	0.023	0.623
CD16 percent	−0.054	0.658	0.030	0.530	0.025	0.838	0.024	0.613
CD38 on CD8	0.039	0.660	−0.060	0.399	0.023	0.793	−0.085	0.230
Total testosterone	−0.097	0.245	0.037	0.804	−0.081	0.340	0.155	0.275
Free testosterone	−0.147	0.085	0.034	0.759	−0.072	0.407	0.079	0.459

Measure	Fatigue intensity				Fatigue-related impairment of functioning			
	Effect of within-person …				Effect of within-person…			
	Mean		Deviation		Mean		Deviation	
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
DHEA	−0.172	0.045	0.122	0.304	−0.144	0.096	0.195	0.086
Hemoglobin	−0.098	0.242	−0.102	0.182	−0.100	0.231	−0.037	0.629
Hematocrit	−0.071	0.408	−0.092	0.196	−0.086	0.314	−0.033	0.640
Serum erythropoietin[b]	−0.092	0.309	0.053	0.562	−0.037	0.685	−0.016	0.858
Lactic acid	−0.065	0.544	0.003	0.940	−0.024	0.820	−0.021	0.630

[a] Measured at first visit only

[b] Logged for modeling

Table 4

Adjusted effects of psychosocial variables on fatigue intensity

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
Baseline employment status	−0.532	0.002	−0.503	0.002	−0.438	0.005	−0.156	0.268	−0.123	0.428
Baseline income, $\log_{10}$	−0.061	0.073	−0.058	0.076	−0.050	0.106	−0.042	0.117	−0.039	0.174
On ART at baseline	−0.558	0.009	−0.377	0.071	−0.265	0.183	−0.218	0.204	−0.284	0.119
Years since HIV diagnosis at baseline	−0.029	0.018	−0.024	0.041	−0.018	0.107	−0.016	0.108	−0.008	0.437
CD4 count (mean)	−0.106	0.187	−0.088	0.256	−0.096	0.188	−0.097	0.122	−0.096	0.152
CD4 count (deviation)	−0.076	0.486	−0.057	0.597	−0.054	0.618	−0.099	0.342	−0.095	0.371
HIV RNA viral load, $\log_{10}$ (mean)	−0.106	0.307	−0.080	0.424	−0.067	0.479	−0.103	0.207	−0.118	0.175
HIV RNA viral load, $\log_{10}$ (deviation)	0.007	0.900	0.014	0.796	0.012	0.825	−0.003	0.960	0.012	0.817
Number of childhood traumas	0.121	0.004	0.091	0.026	0.068	0.085	0.063	0.060	0.078	0.029
Number of stressful events (mean)			0.308	< 0.001	0.216	0.018	0.135	0.088	0.167	0.046
Number of stressful events (deviation)			0.096	0.023	0.103	0.017	0.080	0.048	0.070	0.095
Baseline social support			−0.115	0.094	−0.065	0.327	−0.042	0.462	0.023	0.717
Davidson PTSD score (mean)					0.307	< 0.001				
Davidson PTSD score (deviation)					0.079	0.135				
HADS anxiety score (mean)							0.568	< 0.001		
HADS anxiety score (deviation)							0.242	< 0.001		
Beck Depression Inventory score (mean)									0.535	< 0.001
Beck Depression Inventory score (deviation)									0.212	< 0.001

Table 5

Adjusted effects of psychosocial variables on fatigue-related impairment of functioning

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
Baseline employment status	−0.499	0.004	−0.457	0.005	−0.388	0.012	− 0.153	0.297	−0.080	0.602
Baseline income, $\log_{10}$	−0.090	0.009	−0.088	0.006	−0.080	0.009	−0.073	0.009	−0.069	0.016
On ART at baseline	−0.420	0.049	−0.211	0.305	−0.094	0.631	−0.072	0.687	−0.120	0.505
Years since HIV diagnosis at baseline	−0.026	0.034	−0.022	0.058	−0.016	0.155	−0.015	0.152	−0.006	0.545
CD4 count (mean)	−0.040	0.625	−0.024	0.755	−0.033	0.645	−0.033	0.614	−0.033	0.622
CD4 count (deviation)	0.031	0.772	0.049	0.644	0.053	0.617	0.008	0.940	0.017	0.868
HIV RNA viral load, $\log_{10}$ (mean)	−0.076	0.466	−0.055	0.574	−0.041	0.656	−0.076	0.374	−0.093	0.280
HIV RNA viral load, $\log_{10}$ (deviation)	−0.028	0.600	−0.022	0.682	−0.025	0.646	−0.039	0.455	−0.023	0.658
Number of childhood traumas	0.106	0.012	0.069	0.088	0.043	0.272	0.044	0.206	0.056	0.113
Number of stressful events (mean)			0.305	< 0.001	0.206	0.022	0.154	0.062	0.165	0.047
Number of stressful events (deviation)			0.090	0.029	0.094	0.025	0.075	0.062	0.068	0.102
Baseline social support			−0.196	0.004	−0.144	0.029	−0.134	0.024	−0.061	0.337
Davidson PTSD score (mean)					0.325	< 0.001				
Davidson PTSD score (deviation)					0.080	0.123				
HADS anxiety score (mean)							0.499	< 0.001		
HADS anxiety score (deviation)							0.242	< 0.001		
Beck Depression Inventory score (mean)									0.532	< 0.001
Beck Depression Inventory score (deviation)									0.181	0.003