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Physiological Correlates of HIV-Related Fatigue

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Abstract

Our primary aim is to describe the relationship of multiple physiological variables and HIV-related fatigue. We report baseline data collected from 128 human immunodeficiency virus (HIV)-positive individuals. The HIV-Related Fatigue Scale was used to measure several aspects of fatigue. Blood was drawn for the following physiological variables: hepatic function, thyroid function, HIV viral load, immunologic function, gonadal function, hematologic function, serum cortisol, and cellular injury. In bivariable analyses, free testosterone ($p = 0.03$) and CD8 ($p = 0.07$) were negatively correlated with fatigue intensity, and nonlinear relationships were observed between fatigue intensity and total testosterone ($p = 0.02$), thyroxine ($p = 0.01$), hematocrit ($p = 0.06$), and total bilirubin ($p = 0.06$). However, none of these associations persisted in multivariable models. It is possible that fatigue suffered by seropositive people is better predicted by other variables, which must be better understood to develop interventions to successfully ameliorate HIV-related fatigue.

Keywords

HIV-related fatigue; physiological variables; biomarkers

Now that treatments are available to prolong the lives of people with human immunodeficiency virus (HIV) infection, symptom management has become an increasingly pressing concern. The most frequent and debilitating complaint of HIV-positive people is fatigue, defined as "awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity" (Aaronson et al., 1999, p. 46). Justice, Rabeneck, Hays, Wu, and Bozzette (1999) found fatigue to be the most common symptom among people with HIV infection; fatigue was associated with functional limitation and greater fatigue predicted lower chances of survival. Some researchers speculate that HIV-related fatigue is a result of physiological factors, whereas others argue that it is a function of psychosocial variables. This report focuses on the relationship of physiological variables and HIV-related fatigue.

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Problem

Several researchers have looked at physiological correlates of fatigue in seropositive persons. Lower CD4 count has been related to greater fatigue in some studies (i.e., Darko, McCutchan, Kripke, Gillin, & Golshan, 1992; Lee, Portillo, & Miramontes, 1999; Walker, McGown, Jantos, & Anson, 1997), but not in others (i.e., Barroso, Carlson, & Meynell, 2003; Breitbart, McDonald, Rosenfeld, Monkman, & Passik, 1998; Justice et al., 1999; Perkins et al., 1995; Sullivan, Dworkin, & the Adult and Adolescnt Spectrum of HIV Investigators, 2003; Vlahov et al., 1994; Vogl et al., 1999; Voss, 2002). Henderson, Safa, Easterbrook, & Hotopf (2005) actually found greater fatigue in individuals with higher CD4 counts. Some studies found no relationship between fatigue and HIV viral load (Barroso et al., 2003; Ferrando et al., 1998; Sullivan et al., 2003; Voss, 2002), whereas one found greater fatigue with a higher viral load (Simmonds, Novy, & Sandoval, 2005).

Other immune abnormalities in HIV infection may influence the development and course of fatigue. Untreated HIV infection generally produces a state of heightened immune activation, as measured by CD8CD38 cells, whereas successfully treated patients usually show evidence of decreased immune activation. Differences in the level of immune activation among patients who are on antiretroviral therapy may be independent of HIV RNA level and CD4 cell count (i.e., Bofill & Borthwick, 2000; Deterre et al., 2000; Knapp et al., 2001; Savarino, Bottarel, Malavasi, & Dianzani, 2000; Stuart et al., 2000; Vigano, Saresella, Villa, Ferrante, & Clerici, 2000). Deterre et al. (2000), for example, suggest that changes in $CD38^{+}$ expression may be caused by inflammation, which is often associated with lymphocyte activation. Heightened states of immune activation such as that seen in hepatitis are known to be associated with fatigue (i.e., Bartlett & Gallant, 2000; Koch, Kim, & Friedman, 2001); therefore, it is possible that abnormal immune activation such as that hypothesized in chronic fatigue syndrome is manifested in HIV-positive patients who suffer fatigue.

The physiological abnormalities seen in seropositive persons with fatigue may also reflect damage by the virus to the hematopoietic, hypothalamic-pituitary-adrenal (HPA) axis and/or endocrine systems. Fatigue in HIV infection appears to closely resemble the fatigue seen in chronic fatigue syndrome and fibromyalgia, which reflects HPA axis dysfunction (Patarca-Montero, Antoni, Fletcher, & Klimas, 2001; Teitelbaum et al., 2001). The HPA axis is also adversely affected by psychosocial problems such as anxiety and depression (Kirschbaum & Hellhammer, 1994). Moreover, the high levels of stress that are frequently observed in individuals with HIV infection can increase the activity of the HPA axis: in situations with low predictability and low controllability (such as HIV infection), corticotropin releasing hormones (CRH) and adrenocorticotropic hormones (ACTH) are released, with subsequent rises in cortisol levels (Kirschbaum & Hellhammer, 1994). Thus, mean cortisol levels have been found to be higher in HIV-positive persons than in HIV-negative, healthy control persons (Clerici et al., 1997; Enwonwu, Meeks, & Sawiris, 1996; Rondanelli et al., 1997), and cortisol abnormalities have been implicated as a cause of their fatigue (Clerici et al., 1997; Clerici et al., 2000; Eledrisi & Verghese, 2001; Enwonwu et al., 1996; Piedrola et al., 1996; Stolarczyk et al., 1998). Finally, Andersen et al. (2006) examined the correlation between HIV-related fatigue and cerebral fluorine-18-fluorodeoxyglucose positron emission tomography scanning, to investigate the potential association with systemic inflammation and abnormalities of the distribution of cerebral glucose metabolism, and found no correlation with HIV-related fatigue.

The most common hematologic abnormality seen in patients with HIV infection is anemia, and fatigue is a cardinal symptom of anemia (Groopman, 1998). Anemia may occur as a result of HIV-induced ineffective hematopoiesis, opportunistic infections, infiltrative disease of the bone marrow, nutritional deficiencies, hemolysis, or antiretroviral or other therapy (Breitbart et al., 1998; Ferri et al., 2001; Groopman, 1998; Mocroft et al., 1999; Moore, 1999; Moore,

Keruly, & Chaisson, 1998; Sullivan et al., 1998). Higher hemoglobin levels, even within the conventional normal range, are associated with higher energy scores, higher physical functioning scores, and improved quality of life in individuals with AIDS (Semba, Martin, Kempen, Thorne, & Wu, 2005). Fatigue is also a principal symptom of hypothyroidism, and in one study of HIV-positive persons, thyroid-stimulating hormone (TSH) was found to be abnormally flattened over a 24-hour period rather than showing the variable 24-hour rhythm of healthy individuals (Rondanelli et al., 1997). Barroso et al. (2003) found a negative 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 (Schurmeyer, Muller, Muhlen, & Schmidt, 1997). Some researchers have speculated that the low levels of testosterone (Rabkin, Wagner, & Rabkin, 2000) and low levels of dehydroepiandrosterone (DHEA; Rabkin, Ferrando, Wagner, & Rabkin, 2000) common in people with HIV infection may cause fatigue. Finally, some clinicians have observed fatigue with hepatic dysfunction (Bartlett & Gallant, 2000; Koch et al., 2001), and as noted above, cytokine release could influence hepatic dysfunction. There is a high prevalence of hepatitis C in seropositive people: it is estimated that 300,000 of the 750,000 HIV-infected individuals in the United States are coinfected with the hepatitis C virus (HCV). Anemia, a major cause of fatigue, as noted above, is especially prevalent in HIV/HCV coinfected patients (Ferri, 2002; Kirton, 2002), and those who are coinfected have increased fatigue (Braitstein et al., 2005). These authors concluded, however, that although HIV/HCV coinfected patients experience poorer quality of life, increased depression and fatigue, this experience was related to socioeconomic issues rather than HCV infection.

Purpose

In summary, there are conflicting data regarding possible physiological sources of HIV-related fatigue. This is frustrating for individuals trying to live with it; the fatigue often persists even with immune system restoration and a suppressed HIV viral load. However, few of these studies had fatigue as their primary variable of interest, and none of them examined multiple physiological relationships that might exist with fatigue. In the present article, we investigate the cross-sectional relationship between fatigue and a wide range of physiologic characteristics in a sample of 128 HIV-positive individuals.

Design

This study employs a longitudinal, repeated measures design; we report the baseline data here. Participants have a baseline study visit, then return every 6 months for 3 years, for a total of seven study visits. At the 3-month point between study visits, we mail the HIV-Related Fatigue Scale (HRFS) to them, to monitor their fatigue more closely.

Sample

Any HIV-positive individual 21 years and older who could read and speak English and was mentally competent to provide reliable data (as determined via telephone interview with the principal investigator) was considered eligible for the study. Between March 2005 and May 2006, we enrolled 128 fatigued and nonfatigued persons. Persons with a comorbid condition marked by fatigue such as renal disease, cancer, or multiple sclerosis were excluded, as were pregnant women and those women less than 12 months postpartum. Flyers advertising the study were distributed at several HIV/AIDS treatment centers that typically see a referral population and at the offices of an AIDS service organization in a southern state. Although fatigue was prominent on the flyer, we stated that we were searching for both fatigued and nonfatigued people. The Institutional Review Board at a major academic medical center

approved the study protocol, and written informed consent was obtained from each participant; each was given a copy of the signed consent form.

Method

Persons interested in participating in the study contacted the principal investigator who conducted the preliminary screenings by telephone. Potential participants were then contacted by one of the two study coordinators and an initial visit was scheduled. The study visits were conducted at the General Clinical Research Center (GCRC) of an academic medical center. Participants were encouraged to take breaks whenever they became tired. Participants were paid $70 for the study visit, which included reimbursement for transportation costs.

Baseline demographic data were collected at the first study visit by one of two research assistants during face-to-face interviews with study subjects. An investigator-developed form was used to collect demographic data including age, sex, race/ethnicity, employment status, income, medications (including antiretrovirals, antidepressants, and anxiolytics), and HIV-related illnesses (categorized into B or C illnesses using the Centers for Disease Control guidelines [CDC, 1992]).

The HRFS (Barroso & Lynn, 2002) was used to measure several aspects of fatigue. It is a Likert-type self-report measure with the following scales, each ranging from 1 to 10: fatigue intensity (8 items, Cronbach's alpha 0.93) and impact of fatigue on daily functioning (22 items, Cronbach's alpha 0.98), with the latter divided into three subscales: impact of fatigue on activities of daily living (ADL; 12 items, Cronbach's alpha 0.96), impact of fatigue on socialization (6 items, Cronbach's alpha 0.93), and impact of fatigue on mental functioning (4 items, Cronbach's alpha 0.93). A higher score on scales and items indicates more intense fatigue or greater adverse impact of fatigue. Responses range either from 1 to 7 or 1 to 10 depending on the question; the former were rescaled to range from 1 to 10 before computing summary scales as described below. The HRFS has a 7th-grade reading level. 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 subjects being fatigued. Therefore, the few subjects with virtually no fatigue ($n = 15$) are given a 1 on all scales, subscales, and individual items.

After completion of questionnaires, blood was drawn from participants to measure the following at baseline: hepatic function (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase [GGT], alkaline phosphatase, total bilirubin, 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).

Data Analysis

We report means and standard deviations of all measured physiologic variables. We used ordinary least squared regression to calculate bivariate associations between each physiologic variable and the two primary fatigue scales (fatigue intensity and fatigue-related impairment of functioning); results are reported as standardized coefficients (that is, the coefficient corresponds to the expected change in each fatigue scale, on a 1 to 10 scale, associated with a one-standard-deviation change in the physiologic variable). We further considered multivariable linear regression models, developed in two stages for each scale. First, we entered all sociodemographic (gender, race, employment, and income) and clinical variables (current antiretroviral therapy; other chronic illnesses; current antidepressant use; years since HIV diagnosis; and for functioning scale only, current alcohol problems) that had $p < 0.20$ in

bivariable analyses and retained only those predictors that remained statistically significantly associated with the relevant scale at $p < 0.05$. Second, we added all physiologic variables that had a bivariable $p < 0.20$. In all models we verified the key assumptions (homoskedasticity, normal distribution of the outcome variable). We confirmed the assumption of linearity for continuous variables by comparing a simple linear specification to a restricted quadratic spline with three knots and by visually inspecting locally weighted scatterplot smoothing (lowess) graphs.

Findings

The baseline sociodemographic and clinical characteristics of the study sample are described in Table 1. The majority of subjects were African American ($n = 84$, 66%), followed by Caucasian ($n = 39$, 30%); 4% ($n = 5$) were other ethnic minorities (i.e., Hispanic, Native American). Sixty-six percent ($n = 84$) of the subjects were male (no one self-identified as trans-gendered), and the median age was 44 years old. 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 to 25 years). With regard to HIV-related illnesses, 9% ($n = 12$) of subjects had experienced a CDC Category B illness, and 17% ($n = 22$) had experienced a CDC Category C illness. A large number ($n = 105$, 82%) of subjects were on anti-retroviral therapy at baseline. The mean score for level of fatigue most days was 4.9, and the mean score for fatigue severity in the week prior to the first study visit was 5.6 (each on a 1 to 10 scale).

Table 2 presents the means and standard deviations of the physiological variables, and their correlations with fatigue intensity and fatigue-related impairment of functioning. Our sample was extraordinarily ordinary from a physiological standpoint. The mean CD4 count, an indicator of damage done to the immune system by the virus, was 517/mm^3 (normal range is 400 to 1,400). The mean HIV viral load, an indicator of the amount of virus in the blood, was 17,017 copies/ml (mean log 10 viral load was 2.95); viral loads can range from undetectable to greater than 750,000 copies/ml. All other labs had means that were within normal ranges, with the exception of GGT (mean of 79 U/L; lab normal range is 8 to 55 U/L), and the percentage of CD38 markers on CD8 cells (68% of the CD8 cells expressed CD38 markers). With a group that is as immunologically robust as this one is, one would expect the CD38 markers to be lower. Baseline physiological variables found to be associated with fatigue intensity in bivariable analyses included CD8 ($\beta = -0.362$, $p < 0.10$), and free testosterone and fatigue intensity ($\beta = -0.419$, $p < 0.05$). Variables associated with fatigue-related impairment of functioning included CD8 ($\beta = -0.467$, $p < 0.05$), and DHEA ($\beta = -0.366$, $p < 0.10$). None of the physiological variables was significantly correlated with any of the fatigue scales or subscales in multivariate linear regression after controlling for the retained demographic (income) and clinical factors (years since HIV diagnosis; data not shown).

Discussion and Application

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-positive individuals generally. Self-reported measures of fatigue may be subject to misclassification which, if nondifferential by other covariates, would tend to bias estimates of association toward the null.

The literature on HIV-related fatigue offers conflicting evidence on whether physiological variables predict fatigue. We found in this sample that physiological variables did not predict and are insufficient in explaining HIV-related fatigue. Therefore, we would expect

psychosocial and other clinical factors to be important correlates of fatigue, and in future analyses we will explore the relationship between psychosocial variables and fatigue. Just as there is research to support a physiological cause of HIV-related fatigue, there are studies which indicate that psychosocial factors (most notably depression) may be implicated. We will be examining these data to help us better understand this phenomenon.

Because most of the sample has at least moderate fatigue, what we may be observing is that among those fatigued, severity of fatigue is not associated with any of these lab markers. Also, research to date on physiologic predictors of HIV-related fatigue has used a standard biomedical approach in which subjects must have lab values outside the normal range to be considered abnormal. With a symptom as complex as fatigue, this approach may not be appropriate: it may be *change* in lab values, even within normal ranges, that makes the difference between a nonfatigued state and a fatigued state or an increase in fatigue. Also, change in several variables, even if the values are still within the normal range, may produce a fatigued state. For example, a 3-gram drop in hemoglobin accompanied by a 4-μg drop in thyroxine may be sufficient to cause fatigue even if the new values are still within the normal ranges. We will examine changes in multiple lab values over time, because we will be following this group for 3 years, to determine their relationships to the development of fatigue. Another question is related to the elevated CD8CD38 value. CD38 expression on CD8 is indicative of a poor outcome even with CD4 rebound, as an indicator of residual viral replication (Chun et al., 2004). In successfully treated patients, CD8CD38 markers prior to treatment were 67%; after treatment, they were 47% (Li et al., 2004). Above all, the most valuable data will be obtained from a longitudinal examination of all of these factors, to see what changes prior to a worsening of HIV-related fatigue. Only then will we be able to develop effective nursing interventions to ameliorate HIV-related fatigue.

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Jane Leserman, PhD, is a medical sociologist and professor in the departments of psychiatry and medicine at the University of North Carolina–Chapel Hill. Her areas of multidisciplinary research include the psychoneuroimmunology of HIV infection (e.g., the effects of trauma on HIV disease progression), and the effects of stressful life events and trauma on the health of patients with chronic unexplained pain (e.g., functional gastrointestinal disorders, chronic pelvic pain).

Table 1

Demographic and Clinical Characteristics of Sample (N = 128)

Characteristic	*n* (%) or Median (IQR)
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	50 (39.1%)
Heterosexual sex	42 (32.8%)
IDU	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%)
Primary caregiver for another	19 (14.8%)
Number of household members	2 (1–3)
Years since HIV diagnosis (range: 0–25)	10 (6–15)
On any antiretroviral therapy	105 (82.0%)
Any HIV-related illness	
CDC Category B	12 (9.4%)
CDC Category C	22 (17.2%)
Any other chronic illnesses	83 (64.8%)
Current psychotropic medication use	53 (41.4%)
Antidepressant	50 (39.1%)
Anxiolytic	19 (14.8%)
Ever used street drugs	98 (76.6%)
Ever used nonmarijuana drugs	84 (65.6%)
Currently using street drugs	28 (21.9%)
Ever injected street drugs	26 (20.3%)
Current alcohol problem	12 (9.4%)
Currently in pain	58 (45.3%)
Pain on 1–10 scale	7 (5–8)

Note: IQR: Interquartile range (25th to 75th percentile). MSM: Men who have sex with men. IDU: Injection drug use.

Table 2

Means and Standard Deviations of the Physiologic Variables and Correlations of Physiologic Measures With Fatigue Intensity and Fatigue-Related Impairment of Functioning

Measure	*n*	Mean ± *SD*	Range	Standardized Coefficient[b]	
				Fatigue Intensity[c]	Fatigue-Related Impairment of Functioning[c]
Hepatic function					
Aspartate aminotranspertase	125	39.54 ± 23.48	12–153	0.075	−0.237
Alanine aminotranspertase	125	40.69 ± 29.48	11–154	−0.064	−0.203
Gamma glutamyl transpeptidase[a]	124	78.69 ± 87.00	7–537	−0.006	0.004
Alkaline phosphatase	125	99.45 ± 38.80	50–287	0.256	−0.110
Total bilirubin[a]	125	0.65 ± 0.70	0.09–4.10	−0.176	0.242
Hepatitis C status (dichotomous)	127	0.25 ± 0.44	0–1	0.106	−0.281
Thyroid function					
Thyroid-stimulating hormone	127	1.59 ± 1.53	0.33–16.45	−0.305	0.238
Thyroxine	128	0.73 ± 0.12	0.49–1.21	0.164	−0.106
HIV RNA viral load[a]	128	17071 ± 72729	<50–>750,000	0.285	−0.038
Immunologic function					
CD4 count	128	517.52 ± 342.98	29–1755	−0.242	−0.019
CD4 percent	128	24.31 ± 11.48	3–54	−0.287	0.019
CD8	125	1063 ± 524	294–2767	−0.362[+]	−0.467[*]
T4/T8 ratio[a]	125	0.84 ± 2.50	0.04–28.00	−0.080	−0.080
CD16 count	124	47.16 ± 80.96	0–499	0.058	−0.230
CD16 percent	124	2.30 ± 3.37	0–20	−0.026	0.171
CD38 on CD8	125	68.64 ± 15.11	38–97	0.064	0.045
Gonadal function					
Total testosterone	128	388.49 ± 324.66	7–1630	−0.184	−0.312
Free testosterone	124	8.77 ± 7.30	0.09–32.1	−0.419[*]	−0.253
Dehydroepiandrosterone	127	118.32 ± 88.49	14–421	−0.305	−0.366[+]
Hematologic function					
Hemoglobin	127	14.23 ± 1.81	9.8–19	−0.213	−0.201
Hematocrit	127	0.43 ± 0.05	0.3–0.55	−0.127	−0.224
Serum erythropoietin[a]	126	18.25 ± 27.87	2.9–289	−0.025	−0.023
Cellular injury					
Lactic acid	127	76.16 ± 8.84	43–92	−0.096	−0.175

[a] Log-transformed in regression models to reduce skew.

[b] From bivariate ordinary least squares regression models; coefficients standardized to represent the expected change in fatigue score associated with a one-standard-deviation change in the physiologic measure.

[c] Fatigue scores could range from 1 to 10.

[+] $p < 0.10$.

[*] $p < 0.05$.