

Chronicity and Remission of Fatigue in Patients with Established HIV Infection

Brian Wells Pence, Ph.D., M.P.H.,¹⁻³ Julie Barroso, Ph.D., A.N.P., A.P.R.N., B.C.,⁴
James L. Harmon, R.N., M.S.N., A.N.P.,⁴ Jane Leserman, Ph.D.,⁵
Naima Salahuddin, R.N., M.S.N.,⁴ and Bradley G. Hammill, M.S.⁶

Abstract

Fatigue is one of the most common and debilitating complaints of HIV-positive individuals, potentially leading to important functional limitations. We recruited 128 HIV-positive individuals (fatigued and nonfatigued) between March 2005 and May 2006; 66% were male, 66% were African American, 45% had greater than a high school education, 67% were unemployed, and ages ranged from 26–66 (median, 44). Every 3 months for 15 months, participants completed a 56-item self-report fatigue scale developed and validated by the authors. Participants were classified as fatigued or not fatigued at each assessment and received scores for fatigue intensity and impact of fatigue on functioning. We used linear mixed-effects models to assess longitudinal variation in fatigue scores and generalized estimating equations for binary outcomes to model predictors of fatigue remission among those fatigued at baseline. At baseline, 88% of the sample was fatigued. Fatigue measures were highly correlated across time points (ρ 0.63–0.85 [intensity], 0.63–0.80 [functioning]) and showed no evidence of overall improvement, deterioration, or convergence over time. Predictors of lower fatigue scores included higher income, employment, longer time since HIV diagnosis, and antiretroviral therapy use. Those employed at baseline were likely to show improvements in fatigue while those unemployed were not. Of those fatigued at baseline, 11% experienced remission during follow-up; remission was associated with Caucasian race and employment. In summary, fatigue intensity and related functional limitations were persistent, stable, and unlikely to remit over 15 months of follow-up in this sample of patients with established HIV infection.

Introduction

IN THE PRESENT ERA of long-term medical management of HIV infection, fatigue has emerged as one of the most common and debilitating complaints of people infected with HIV. Estimates of the prevalence of fatigue in HIV-positive individuals when measured by self-report generally range from 55% to 65%, with similar estimates reported both before and since the advent of highly active antiretroviral therapy.¹⁻⁵ While some develop fatigue early in HIV infection, others develop fatigue with disease progression.⁶ The consequences of fatigue include having to stop working, limiting one's involvement with family and friends, being unable to manage one's finances, and needing an entire day to get through the simplest of household chores.⁷⁻⁹ Justice et al.¹⁰ found that fatigue was the most common symptom among people with

HIV infection, reported by 67% of respondents, and that fatigue was associated with functional limitation and higher mortality.

Despite the clinical and functional relevance of fatigue, little research has been published regarding the persistence and remission of fatigue in HIV-positive individuals. The natural variation in fatigue symptoms over time and the propensity of fatigue to remit in the absence of direct intervention are questions of some importance for the clinical management of patients with HIV infection.

Accordingly, in the present study, we completed detailed assessments of the intensity of fatigue and the impact of fatigue on daily functioning over 15 months of follow-up in a sample of patients with established HIV infection to assess the natural course of fatigue and the predictors of fatigue remission.

¹Health Inequalities Program, Center for Health Policy, ²Global Health Institute, ³Department of Community and Family Medicine, ⁴School of Nursing, ⁶Center for Clinical and Genetic Economics, Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina.

⁵Department of Psychiatry, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Methods

Sample and procedures

We report results from a prospective observational cohort study of the causes and consequences of fatigue in HIV-positive individuals that has been described in detail previously.¹¹ Participants were recruited via flyers advertising the study at HIV/AIDS treatment centers and service organizations in a small metropolitan area of a southern state. While fatigue was prominent on the flyer, we stated that we were searching for both fatigued and nonfatigued people. Interested individuals were invited to participate if they met the following inclusion criteria: (1) HIV-positive, (2) 21 years or older, (3) able to read and speak English competently, and (4) judged mentally competent to provide reliable data by the principal investigator (J.B.). Both fatigued and nonfatigued individuals were eligible to enroll. Individuals were excluded if they had a comorbid condition marked by fatigue such as renal disease, cancer, or multiple sclerosis. Pregnant women and women less than 12 months postpartum were also excluded. Of the 150 interested individuals who expressed interest and met eligibility criteria, 128 (85%) enrolled in the study and completed the baseline assessment between March 2005 and May 2006.

Participants attended study visits in the General Clinical Research Center of an academic medical center at baseline and at 6-month intervals thereafter. At these visits, participants completed assessments of fatigue, sleep quality, depression, anxiety, symptoms of posttraumatic stress disorder, stress, social support, common medical symptoms, and general health. Participants also provided a blood sample for the quantification of a range of biomarkers of hepatic, thyroid, immunologic, gonadal, and hematologic function as well as HIV viral load, serum cortisol, and cellular injury; all laboratory results were provided to the treating clinician for any necessary clinical follow-up. At baseline, additional information about demographics and lifetime trauma exposure were collected. Supplemental fatigue assessments were completed at home at the midpoint between study visits and mailed in. Participants received \$70 in compensation for each study visit and \$20 for completing each fatigue questionnaire by mail. Data available for this analysis extended through 15 months of follow-up, comprising 3 in-person fatigue assessments (0, 6, and 12 months) and 3 assessments by mail (3, 9, and 15 months). All study procedures were approved by the Duke University Institutional Review Board, and all study participants provided written informed consent.

Measures

Fatigue. The HIV-Related Fatigue Scale (HRFS),¹² a Likert-type 56-item self-report measure with a seventh-grade reading level, was used to measure fatigue intensity, the impact of fatigue on functioning, and the circumstances surrounding fatigue. In psychometric assessments, the HRFS demonstrated high internal consistency and satisfactory convergent validity when compared with other measures of fatigue and related constructs.¹³ The 8-item fatigue intensity scale of the HRFS (Cronbach α 0.93) includes Likert scale-rated items such as the respondent's level of fatigue today and most days, the severity of the fatigue, and the extent to which fatigue has caused problems or distress. The 22-item scale measuring

the impact of fatigue on daily functioning (Cronbach α 0.97) asks about the extent to which fatigue has impaired activities of daily living (ADLs; e.g., cooking, bathing, dressing, exercising), socialization (e.g., visiting/socializing, interactions with others outside home, sexual activity), and mental functioning (e.g., thinking clearly, concentration). Both the intensity of fatigue and its impact on functioning are of clinical relevance: some subjects may be very fatigued, but are able to minimize its impact on their cognitive and social functioning and the completion of activities of daily living. Higher scores indicate more intense fatigue or greater impact of fatigue; each scale ranges from 1 to 10. Although we conceptualize fatigue intensity and impairment of functioning as continuous rather than categorical constructs, for descriptive purposes we also examined the proportion of individuals scoring 7 or more on each scale as a proxy for severe fatigue and impairment.

Subjects whose intensity of fatigue was low (1 or 2 out of 10) on all of the first 7 HRFS items (e.g., my level of fatigue today; my level of fatigue on most days; how severe is the fatigue) were coded as not fatigued at that time point and were assigned a value of 1 on all remaining items. Among those presenting as fatigued at baseline, we classified any individual presenting as not fatigued at a later time point as experiencing remission at that time.

Other variables. Patients reported sociodemographic and certain clinical information (e.g., age, race, education, when diagnosed with HIV infection, and current antiretroviral therapy [ART] status) in interviews with one of two research assistants. Plasma samples were analyzed using standard methods to measure CD4⁺ cell count and HIV RNA viral load (VL).

Analyses

We used analytic methods appropriate for repeated observations with normally distributed and dichotomous dependent variables. We used linear mixed-effects models to assess (1) the overall trend in fatigue scores over time, (2) individual and group variation in fatigue score trajectories, and (3) predictors of fatigue scores. We used likelihood ratio tests with appropriate mixed χ^2 distributions¹⁴ that compared nested models to assess whether inclusion of random intercepts (indicating individual variation in overall fatigue levels) and random slopes (indicating individual variation in fatigue trajectories over time) contributed to the fit of the models. We used interaction terms with time to assess whether there were differences in fatigue trajectories between groups.

Among those patients presenting with fatigue at baseline, we used generalized estimating equation (GEE) models with a logit link, binomial error distribution, and exchangeable working correlation structure to examine predictors of fatigue remission at subsequent visits. Because remission was a relatively rare event, we used a two-stage model building process to avoid overfitting. First, two groups of covariates were considered in separate models: sociodemographic (age, gender, race, years of education, log-transformed income, and employment status) and clinical (years since HIV diagnosis, ART status, and CD4 count). Viral load was not included in multivariable models due to high correlation with ART status. Covariates with a p value <0.20 in each model were then combined. All models further included baseline fatigue in-

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)
HIV risk factor:	
MSM	50 (39.1%)
Heterosexual sex	42 (32.8%)
IDU	12 (9.4%)
Other/multiple/don't know	24 (18.8%)
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 ^a	11 (10.7%)

^aOf 103 participants fatigued at baseline and with at least one follow-up visit. IQR, interquartile range.

tensity score, time since baseline, and assessment method (in-person versus mail-in fatigue assessment).

Results

Description of sample

The demographic characteristics of the sample reflect the HIV epidemic in the southeastern United States. Participants

were primarily between 30 and 50 years of age. Approximately two thirds of participants were male and approximately two thirds were African American, with the remainder predominantly Caucasian (Table 1). Over half the sample had a high school education or less, and only one third was employed at baseline. Primary HIV risk factors included being a man who had sex with men (39%) and heterosexual contact (32%), with injection drug use playing a relatively minor role in this population (9%). The sample primarily comprised people who had lived with HIV infection for a long time, with a median of 10 years since diagnosis (range, 0–25 years). A large majority was on antiretroviral therapy at baseline and had high CD4 counts and HIV RNA viral loads less than 400 copies per milliliter. Eighty-eight percent of the sample was fatigued at baseline.

Fatigue over time

Retention between 3 and 15 months ranged between 78% and 88% (Table 2). Of the 15 participants (12%) who did not complete the most recent in-person interview (at 12 months), 1 had died, 2 had moved away from the area, 3 had requested to withdraw from the study, and 9 could not be located. Baseline values for fatigued versus nonfatigued status, fatigue intensity, and fatigue-related impairment of functioning did not predict retention at any time point. Men were more likely to complete follow-up than women at 3 and 6 months but this difference was no longer evident at later time points. Those reporting a current alcohol problem were less likely to be retained at some time points (3, 6, 15 months) but not others (9 and 12 months).

Overall, the average level of fatigue intensity in the sample remained relatively stable over 15 months of follow-up, ranging between 5.6 and 6.1 on a 1–10 scale (Table 2). Between 30% and 43% of individuals reported fatigue intensity 7 or greater at each time point. The average level of impact of fatigue on functioning ranged between 4.8 and 5.3 over the same period, with 23%–27% of participants scoring 7 or greater at each time point. For both scales, slightly higher fatigue scores were reported on the mail-in surveys (months 3, 9, and 15) than at in-person visits (months 0, 6, and 12), and the average fatigue level fell slightly from baseline to the 6-month visit but remained stable between the 6- and 12-month visits.

If fatigue were highly variable over time, we would expect to see convergence over time between those who had the highest and lowest fatigue scores at baseline. Instead, participants'

TABLE 2. CHANGES IN FATIGUE INTENSITY AND IMPACT OF FATIGUE ON FUNCTIONING OVER 15 MONTHS OF FOLLOW-UP

Assessment	n	Fatigue intensity ^a		Impact of fatigue on functioning ^a	
		Mean (SD)	% scoring ≥ 7	Mean (SD)	% scoring ≥ 7
Baseline	126	5.85 (2.17)	30.2	5.10 (2.44)	24.6
3-month mail-in	113	6.14 (2.36)	43.4	5.29 (2.33)	27.0
6-month visit	109	5.57 (2.37)	34.9	4.78 (2.57)	21.1
9-month mail-in	100	6.00 (2.43)	39.0	5.16 (2.39)	26.0
12-month visit	111	5.61 (2.33)	33.9	4.86 (2.47)	23.2
15-month mail-in	107	5.95 (2.34)	41.1	5.33 (2.37)	27.1

^aMeasured on a 1–10 scale. SD, standard deviation.

initial fatigue scores were highly predictive of the course of their fatigue over the subsequent 15 months. Figure 1A and 1B show scores for fatigue intensity and impact of fatigue on functioning over time, separated by quintile of baseline fatigue. While some regression to the mean was evident over the first three months, the differences between the quintiles remained remarkably stable between months 3 and 15. The individuals with fatigue scores in the lowest quintile at baseline (mean intensity 2.34) had a mean intensity score of 3.34 at 3 months and the same mean at 15 months. The individuals with fatigue scores in the highest quintile at baseline (mean intensity 8.44) improved slightly to a mean intensity score of 8.11 at 3 months and 7.81 at 15 months. Indeed, correlations between fatigue measures at the 6 time points were universally high, ranging between 0.63–0.85 for fatigue intensity and between 0.63–0.80 for impact of fatigue on functioning (Table 3).

In multivariable linear mixed-effects models, there was no evidence of change over time in the sample's mean fatigue scores (intensity: $\beta = -0.01$ [95% confidence interval {CI} $-0.03, 0.01$] per 6 months; impact of fatigue on functioning: $\beta = 0.00$ [$-0.02, 0.02$]; Table 4). Predictors of overall lower fatigue scores included higher income, employment, longer time since HIV diagnosis, and receipt of antiretroviral therapy. As expected, there was evidence of individual variation in overall fatigue levels on both scales, as indicated by likelihood ratio tests evaluating the contribution of random intercepts to the mixed-effects model (p values <0.001 for both scales). There was no evidence of individual variation in trajectories of impact of fatigue on functioning over time, as indicated by a likelihood ratio test evaluating the contribution of random slopes to the model ($p = 0.91$). However, there was evidence of individual variation in trajectories of fatigue intensity over time ($p = 0.03$). Most of the individual predicted changes were relatively small in magnitude, ranging from a minimum of a 1.7-point predicted decrease to a maximum of a 0.8-point predicted increase in fatigue intensity over 15 months (interquartile range: -0.5 to 0.2).

We found little evidence of variation in fatigue trajectories between groups defined by sociodemographic or clinical characteristics. Only for employment status was an interaction term with time statistically significant. Individuals employed at baseline tended to achieve small improvements in

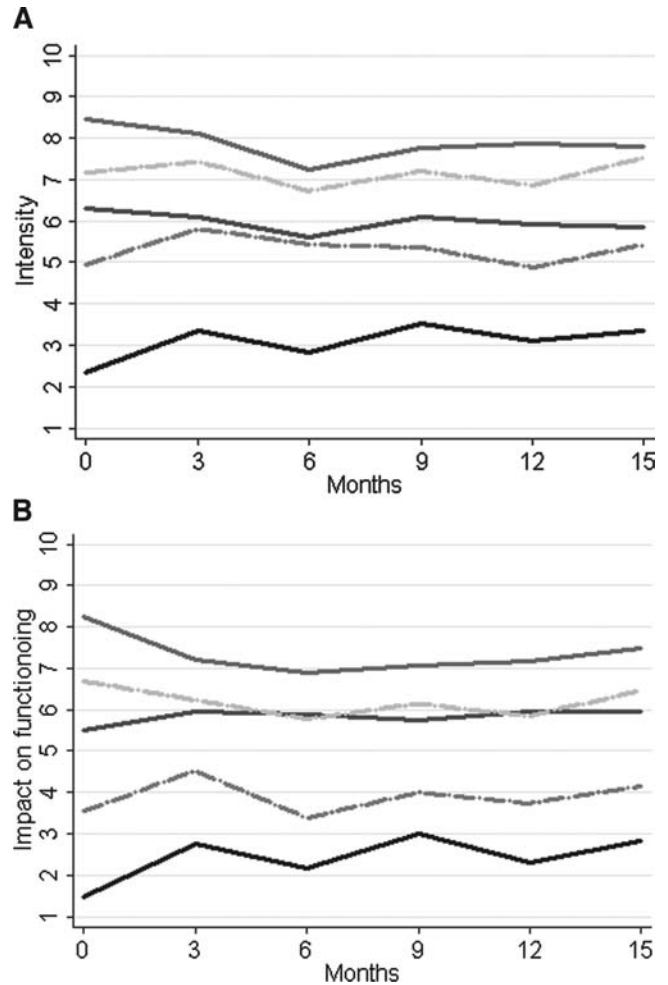


FIG. 1. Fatigue intensity (A) and impact of fatigue on functioning (B) over 15 months of follow-up, by quintile of baseline fatigue.

fatigue intensity (-0.29 [$-0.48, -0.10$]) and impact on functioning (-0.21 [$-0.42, 0.00$]) over time whereas those unemployed did not (0.03 [$-0.10, 0.17$] and 0.08 [$-0.07, 0.23$]; data not shown). For all other groups, average scores for fatigue

TABLE 3. CORRELATIONS BETWEEN REPEATED FATIGUE MEASURES OVER 15 MONTHS

	Baseline	3 months	6 months	9 months	12 months	15 months
Fatigue intensity						
Baseline	1.00					
3 months	0.72	1.00				
6 months	0.67	0.73	1.00			
9 months	0.63	0.73	0.75	1.00		
12 months	0.70	0.76	0.78	0.79	1.00	
15 months	0.70	0.73	0.78	0.80	0.85	1.00
Impact of fatigue on functioning						
Baseline	1.00					
3 months	0.67	1.00				
6 months	0.71	0.65	1.00			
9 months	0.65	0.63	0.71	1.00		
12 months	0.72	0.65	0.74	0.72	1.00	
15 months	0.72	0.70	0.78	0.69	0.80	1.00

TABLE 4. MULTIVARIABLE LINEAR MIXED MODELS OF FATIGUE INTENSITY AND IMPACT ON FUNCTIONING OVER 15 MONTHS

Predictor	Intensity		Impact on functioning	
	Coefficient	95% CI	Coefficient	95% CI
Time since baseline, per 6 months	-0.01	(-0.03, 0.01)	0.00	(-0.02, 0.02)
Mail-in (vs. in-person) assessment	0.39	(0.20, 0.57)	0.36	(0.14, 0.57)
Age, per 10 years	0.19	(-0.26, 0.64)	0.25	(-0.21, 0.70)
Male gender	-0.05	(-0.72, 0.61)	0.28	(-0.39, 0.95)
African American race	-0.05	(-0.73, 0.64)	0.04	(-0.65, 0.73)
Education, per year	-0.04	(-0.18, 0.10)	-0.02	(-0.16, 0.12)
Income, per log ₁₀	-0.43	(-0.77, -0.09)	-0.60	(-0.94, -0.25)
Employed	-1.16	(-1.90, -0.41)	-1.33	(-2.08, -0.58)
Years since HIV diagnosis, per year	-0.06	(-0.12, -0.01)	-0.08	(-0.13, -0.02)
On antiretroviral therapy	-1.10	(-1.89, -0.32)	-0.85	(-1.65, -0.06)
CD4, per 100 cells/mm ³	-0.06	(-0.15, 0.03)	-0.04	(-0.12, 0.05)
Intercept	8.96	(6.32, 11.61)	7.62	(4.94, 10.29)
<i>Random-effects parameters</i>				
Intercepts: SD (95% CI)	1.55	(1.31, 1.83)	1.57	(1.36, 1.81)
Coefficients: time since baseline: SD (95% CI)	0.06	(0.04, 0.10)		
Correlation (95% CI) of intercepts and coefficients	-0.03	(-0.43, 0.38)		
<i>Likelihood ratio test statistics (p value)</i>				
Inclusion of random intercepts	384.39	(< 0.001)	309.82	(< 0.001)
Inclusion of random coefficients (time since baseline)	7.32	(0.016)	0.19	(0.786)

CI, confidence interval; SD, standard deviation.

intensity and impact of fatigue on functioning remained stable over time.

Predictors of remission

Remission of fatigue was a relatively rare event. Of 103 participants who were fatigued at baseline and completed at least one follow-up visit, only 11 were ever classified as not fatigued during 15 months of follow-up. In multivariable GEE models controlling for time and baseline fatigue intensity, individuals of African American race were less likely to experience remission of their fatigue while those employed at baseline were more likely to experience remission (Table 5). Given the small number of remission events, the associated confidence intervals were quite wide.

Discussion

While fatigue is increasingly being recognized as one of the most common and debilitating symptoms accompanying

chronic HIV infection, little longitudinal data exists on the course and persistence of fatigue over time in HIV-infected individuals. In this prospective cohort of patients with long-term HIV infection, we observed a high level of persistence of fatigue, with only 11% of fatigued participants experiencing remission of their fatigue over 15 months of follow-up and with fatigue intensity showing little variation over the same time period. We observed high correlations in fatigue scores measured at 3-month intervals over 15 months: the individuals with the highest fatigue scores at baseline consistently remained the most fatigued over time. We are unaware of any previous research which has described the natural course of HIV-related fatigue over such an extended time period.

The persistence of fatigue has important implications for clinical management. HIV-related fatigue in this sample was unlikely to remit spontaneously in the absence of direct intervention, lending added urgency to efforts to understand the etiology of HIV-related fatigue and to identify intervention points. In baseline analyses from the present study, we identified no associations between fatigue and a wide range of physiological factors.¹¹ In contrast, depression, stress, and traumatic experiences were strongly associated with variation in fatigue levels.¹⁵

Consistent with baseline analyses from this sample, we found that higher income and being employed at baseline were predictive of lower average fatigue levels over the follow-up period. However, the direction of causality cannot be unequivocally determined even from these prospective data given the clear persistence of fatigue over time. This association may indicate that Individuals with more chronic fatigue are less likely to be employed (and therefore have lower incomes), that higher-paying jobs are less physically demanding, or that those with more disposable income are able to hire help to relieve themselves of fatiguing obligations.

TABLE 5. PREDICTORS OF REMISSION OF FATIGUE

Predictor	Remission	
	OR	95% CI
Time since baseline, per 6 months	0.96	(0.88, 1.06)
Mail-in (vs. in-person) assessment	0.54	(0.25, 1.17)
Baseline fatigue intensity score	0.42	(0.26, 0.67)
African American race	0.23	(0.06, 0.80)
Employed	4.30	(1.20, 15.50)
Estimated within-person correlation (exchangeable)	0.26	

OR, odds ratio; CI, confidence interval.

Individuals with more established HIV infection had less fatigue on average, which could reflect the natural history of HIV infection, a survival bias, or the development of coping strategies over time. Receipt of antiretroviral therapy was also associated with less fatigue, although it cannot be determined from these data whether successful management of HIV reduces fatigue or whether individuals with less (or less chronic) fatigue are more likely to receive ART, perhaps because of a greater ability to engage reliably in medical care.

African Americans were only one fourth as likely as those of other races (primarily Caucasians) to experience remission of fatigue during the study period. Although there were no racial differences in scores of fatigue intensity or impact of fatigue on functioning in multivariable analyses, we did observe racial disparities for both scores in bivariable analyses; these differences were eliminated after adjustment for education, income, and employment status. It is possible that the relationship between race and remission is similarly mediated by socioeconomic factors but that the small number of remission events in this analysis made our models of remission unstable. We are unaware of other studies that have described racial disparities in HIV-related fatigue.

It should be noted that the self-referral method of recruitment in this study may have resulted in a sample biased toward individuals with fatigue as well as those with more chronic fatigue. Thus the results of this study may be an overestimate of the prevalence and chronicity of fatigue among HIV-positive individuals generally. Further research on the natural course of fatigue in other samples is warranted. Nevertheless, this analysis indicates that there is at least a subset of HIV patients for whom chronic fatigue is a substantial and enduring concern.

Fatigue remains a challenging construct to measure definitively, with no generally accepted gold standard definition. The HRFS used in this study is a detailed instrument developed through careful formative qualitative research and designed specifically to measure the intensity and consequences of fatigue in HIV-positive individuals.¹² The HRFS has demonstrated strong internal consistency and good convergent and construct validity.¹³

In summary, the present study highlights a high level of stability and persistence of fatigue symptoms over 15 months in a sample of HIV-positive patients. A number of studies have demonstrated the high prevalence and debilitating consequences of fatigue for HIV-positive individuals, and the present study makes clear that at least in a subset of patients, fatigue symptoms are unlikely to resolve on their own. Further attention to understanding the etiology of HIV-related fatigue and identifying intervention points is warranted.

Acknowledgments

This research was supported by the National Institute of Nursing Research, National Institutes of Health, 5R01NR008681 (Julie Barroso, PI), and Grant Number 1UL1RR024128-01 from the National Center for Research Resources (NC\RR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

Author Disclosure Statement

No competing financial interests exist.

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Address reprint requests to:
 Brian Wells Pence, Ph.D., M.P.H.
 Center for Health Policy
 Box 90392
 Duke University
 Durham NC 27705

E-mail: bpence@aya.yale.edu