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Daytime Sleepiness, Nighttime Sleep Quality, Stressful Life Events, and HIV-Related Fatigue

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Abstract

In this report we describe the relationships between daytime sleepiness, nighttime sleep quality, stressful life events, and HIV-related fatigue in a sample of 128 individuals; we are reporting the baseline results of a longitudinal observational study. We examined sleep using the Pittsburg Sleep Quality Index (PSQI) (a measure of the quality of nighttime sleep), and the Epworth Sleepiness Scale (ESS), (a measure of daytime sleepiness). Recent stressful life events were measured via a methodology developed in a previous 9-year HIV study. Poor nighttime sleep was significantly correlated with fatigue intensity ($r = 0.46$, $p < 0.05$), as was daytime sleepiness ($r = 0.20$, $p < 0.05$). However, in multiple regression models, the association between stress and fatigue intensity was not explained by daytime sleepiness and was only partially explained by nighttime sleep quality. Further research is needed to better elucidate these relationships.

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Clinical Considerations
The following may help to improve overall quality of sleep in HIV-infected patients:

- Encourage patients to keep a sleep diary to try to determine what factors are associated with poor sleep.

- Educate patients about good sleep hygiene techniques including: use the bed for sleep or sex only, turn off the television and other sources of sound when trying to sleep, maintain the bedroom at a comfortable temperature.

- Initiate a medication and dietary review with patients:

  - Are they taking SSRIs? When?

  - Are they taking efavirenz?

  - Are they drinking caffeinated beverages after 6 p.m.?

  - Are they snacking late in the evening?

  - Are they using recreational drugs or drinking excessively?

- Assess for symptoms of sleep apnea.

Keywords

daytime sleepiness; HIV-related fatigue; nighttime sleep; stressful life events

The most frequent and debilitating complaint of HIV-infected 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. Prior to the development of interventions to ameliorate HIV-related fatigue, we need to know what factors are associated with it, and how these factors are related to one another. Some researchers have speculated that HIV-related fatigue was a result of physiological factors such as CD4 count and HIV viral load (e.g., Henderson, Safa, Easterbrook, & Hotopf, 2005; Simmonds, Novy, & Sandoval, 2005), while others have argued that it was a function of psychosocial variables such as depression (e.g, Barroso, Carlson, & Meynell, 2003; Voss, 2005). Sleep quality is unique in that poor sleep may have a physiological basis, a psychosocial basis, or a combination of the two.

The first purpose of this article is to examine the relationships among HIV-related fatigue, poor nighttime sleep, and daytime sleepiness. Another relationship of interest is whether sleep quality mediates the stress/fatigue relationship; we have previously reported that stressful life events were strong predictors of HIV-related fatigue intensity and impairment of functioning in this sample (Leserman, Barroso, Pence, Salahuddin, & Harmon, in press). Therefore, the second purpose of this report is to investigate whether the relationship between stress and fatigue is mediated by sleep quality.

HIV-infected individuals often suffer from poor sleep quality, which may contribute to fatigue (e.g., Davis, 2004; Phillips, Mock, Bopp, Dudgeon, & Hand, 2006; Rubinstein & Selwyn, 1998). In a systematic review of 29 studies on insomnia in HIV infection, insomnia was reported frequently and at all stages of HIV infection (Reid & Dwyer, 2005). Darko, McCutchan, Kripke, Gillin, and Golshan (1992) found that HIV-infected patients were significantly more likely than non-infected persons to feel fatigued; HIV-infected patients slept more, napped more, and had diminished midmorning alertness, possibly due to poor nighttime sleep. Robbins, Phillips, Dudgeon, and Hand (2004) found that, among other factors, fatigue was significantly related to sleep quality, and Phillips et al. (2004) found that sleep quality predicted fatigue in HIV-infected subjects. These two reports provided evidence of how closely poor sleep quality and fatigue are related.

Psychosocial factors, such as not having a place to sleep, having to share a bed with too many people, or living in an area in which optimal sleep conditions cannot be achieved (e.g., too hot, too cold, too noisy), can contribute to poor sleep quality as well. Phillips et al. (2004) reported that perceived stress was associated with HIV-related fatigue. However, no studies have examined the impact of stressful life events on HIV-related fatigue, although stressful life events have been associated with fatigue in other diseases (Mancuso, Rincon, Sayles, & Paget, 2005; Van, Egle, & Luyten, 2005). Further examination is needed to determine factors that might mediate the relationship between HIV-related fatigue and poor sleep, and whether sleep quality mediates the stress/fatigue relationship. Here, we report baseline data investigating the cross-sectional relationships between nighttime sleep quality, daytime sleepiness, stressful life events, and HIV-related fatigue, in a sample of 128 HIV-infected individuals who are being followed in a longitudinal observational study.

Methods

Sample

Any HIV-infected individual 21 years of age 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, 128 fatigued and non-fatigued persons were enrolled in the study. Persons with a co-morbid 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 treatment centers that typically cared for a referral population and at the offices of an AIDS service organization in a southern state. While fatigue was prominent on the flyer, it was clear that we were searching for both fatigued and non-fatigued 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.

Procedures

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. 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.

Measures

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 and Prevention guidelines (Centers for Disease Control and Prevention [CDC], 1992).

The HIV-Related Fatigue Scale (HRFS) (Barroso & Lynn, 2002) was used to measure several aspects of fatigue. The HRFS is a Likert-type self-report measure with the following scales, each ranging from 1-10: 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 being 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) (Pence, Barroso, Leserman, Harmon, & Salahuddin, in press). A higher score on scales and items indicates more intense fatigue or greater adverse impact of fatigue. Responses range either from 1-7 or 1-10 depending on the question; the former were rescaled to range from 1-10 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 seven HRFS items (i.e., my level of fatigue today, my level of fatigue on most days, how severe is the fatigue) are told to skip the rest of the instrument because all of the remaining items are dependent on the subjects being fatigued. Therefore, the few subjects with virtually no fatigue ($n = 15$) were given a 1 on all scales, subscales, and individual items.

Nighttime sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a standardized 19-item measure of sleep quality widely used in the literature because of its strong psychometric properties. The seven component scores of the PSQI had an overall reliability coefficient of 0.83, indicating a

high degree of internal consistency. Paired *t* tests were done to evaluate test-retest reliability with an outcome of $r = 0.85$ ($p < 0.001$) for the global PSQI score (Buysse et al., 1989; Carpenter & Andrykowski, 1998). In a comparison study evaluating the psychometric properties of the PSQI across clinical populations, the PSQI global scores were more highly correlated with sleep problems ($r = 0.69$-0.77) in comparison to mood and depression ($r = 0.22$-0.65) (Carpenter & Andrykowski, 1998). This supports the construct validity of the PSQI as a measure of sleep problems and not mood disturbance.

The PSQI was developed specifically to be a brief, easily implemented tool that could distinguish between "good" and "poor" sleepers within a clinical sample. The PSQI asks questions pertaining to the previous month. The seven component scores range from 0 to 3, where 0 indicates no difficulty and 3 indicates severe difficulty; these component scores are then summed for a global score with a range of 0 to 21 points. The seven components of the PSQI are: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. It has been proposed that a PSQI global score of greater than 5 suggests sleep problems (Buysse et al., 1989; Carpenter & Andrykowski, 1998).

The Epworth Sleepiness Scale (ESS) is a brief questionnaire that asks the respondent to rate his/her chances of dozing during the daytime in each of eight different situations (Johns, 2000, 2002), which were selected based on their ability to induce dozing. Each of eight items are ranked from 0 to 3, with a 0 score meaning the respondent would never doze in that situation and a score of 3 equating to a high chance of dozing. Overall scores can vary from 0-24, with a score of 10 or less indicating no pathology. Cronbach's alpha is reported at 0.87, indicating high internal consistency. The reliability of the ESS is similar to the Multiple Sleep Latency Test (MSLT) ($r = 0.81$, $p < 0.001$) (Johns, 2000, 2002).

Recent stressful life events were measured via a methodology developed in a previous 9-year HIV study showing that cumulative stressors predicted faster HIV disease progression (Leserman et al., 1999; Leserman et al, 2000; Leserman et al., 2002). 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 [Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978]). Subjects were then interviewed concerning the nature and context of each of the endorsed stresses. Interviewers objectively rated each stress from 0 (no threat) to 4 (severe threat) using a manual of norms and vignettes, a methodology similar to that developed by Brown and Harris (1978). 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. Two interviewers were trained by one of the investigators and were allowed to rate stresses independently, after reliability with the investigator's ratings was achieved (89-90% agreement, *Kappa* > .83). Periodic reliability checks and retraining were done to insure that the interviewers maintained a high level of consistency. All stresses rated above 1 were summed, except that stressors that were likely to be caused by disease progression (e.g., CD4 count decline, retirement due to HIV worsening) were removed. Stresses rated as 1 were not counted, as these were typically positive stresses or daily hassles (e.g., job promotion).

Data Analysis

In bivariable analyses, Pearson correlation coefficients comparing our measures of fatigue and of sleep quality were calculated. For multiple linear regression models, we standardized both dependent variables (the fatigue intensity scale and the impact of fatigue on daily functioning

scale) and independent variables to have mean 0 and standard deviation 1. Thus, regression coefficients had the interpretation of the change in standard deviation units in the dependent variable that was associated with a one-standard deviation change in the relevant independent variable. For each of the two fatigue scales, we fit three models: the first including stress, the second adding the ESS, and the third adding the PSQI. These models also controlled for important sociodemographic and clinical covariates as has been previously described (Pence, Barroso, Leserman, Harmon, & Salahuddin, in press); in short, we entered all sociodemographic and clinical variables that had a *p* value < 0.20 in bivariable analyses and retained only those predictors that remained statistically significantly associated with the relevant scale at *p* < 0.05 in the multivariable model. We further forced into the model three HIV-related clinical variables deemed substantively important: CD4 count, HIV RNA viral load (log-transformed), and a dichotomous variable indicating whether the participant was on antiretroviral therapy (ART). We confirmed key model assumptions, including normal distribution and homoscedasticity of the dependent variables as well as the appropriateness of linear specifications for continuous independent variables.

Results

The baseline sociodemographic and clinical characteristics of the study sample are described in Table 1. The majority of subjects were African American (66%), followed by Caucasian (30%); 4% were other ethnic minorities (i.e., Hispanic, Native American). Sixty-six percent of the subjects were male, 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 0-25 years). With regard to HIV-related illnesses, 9% of subjects had experienced a CDC Category B illness, and 17% had experienced a CDC Category C illness. A large proportion of subjects (82%) were on ART at baseline. The mean CD4 count was 517 cells/mm^3 (normal range = 400-1400). The mean HIV viral load was 17,017 copies/mL (mean log 10 viral load = 2.95); viral loads can range from below the limit of detection (usually 50 copies/mL) to greater than 750,000 copies/mL. 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 1-10 scale).

The mean Global Sleep Quality Score on the PSQI was 9.4 (*SD* = 4.4) and 80% (103/128) of participants had scores > 5, indicating substantial sleep problems in this group. The PSQI subscale scores were as follows: 47% reported that their overall quality of sleep was fairly bad or very bad; 52% reported trouble getting to sleep; 33% reported 5 or fewer average hours of sleep per night; 26% reported that the average amount of time in bed spent asleep was less than 65%; 66% reported disturbed sleep; 27% reported using sleep medications three or more times a week in the past month; and 42% reported sleep-related daytime dysfunction. The mean score on the ESS was 11 (*SD* = 5.2) with 55% (70/128) of participants scoring > 10. The correlation between the PSQI and ESS was low (*r* = 0.09).

We examined the relationships between the PSQI and ESS scores with two aspects of fatigue: intensity and impairment of functioning. The PSQI total was significantly correlated with fatigue intensity (*r* = 0.46, *p* < 0.05) and fatigue-related impairment of functioning (*r* = 0.47, *p* < 0.05) (Table 2). Correlations between the ESS and fatigue intensity (*r* = 0.20, *p* < 0.05) and fatigue-related impairment of functioning (*r* = 0.33, *p* < 0.05) were of lower magnitude but still statistically significant.

We previously reported that stressful life events were strong predictors of HIV-related fatigue intensity and impairment of functioning in this sample (Leserman, Barroso, Pence, Salahuddin, & Harmon, in press). Here, we investigated whether the relationship between stress and fatigue was mediated by sleep quality. If participants were experiencing a great deal of stress, did the

stress impair their sleep, leading to more fatigue? In multiple regression models, the association between stress and fatigue intensity was not explained by daytime sleepiness and was only partially explained by nighttime sleep quality (standardized beta shifted from 0.26 to 0.22 with addition of PSQI to model and remained statistically significant). The association between stress and fatigue-related impairment of functioning was only marginally explained by daytime sleepiness (beta shifted from 0.28 to 0.26 with addition of ESS to model) and partially explained by nighttime sleep quality (beta shifted to 0.20) but remained statistically significant even after adjustment for both sleep measures.

Discussion

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 nondifferential by other covariates, would tend to bias estimates of association toward the null.

The HRFS subscales were moderately correlated with poor quality nighttime sleep but showed only weak correlations with daytime sleepiness. Poorer quality nighttime sleep, as measured with the PSQI, was moderately associated with greater fatigue intensity and fatigue-related impairment of functioning. In examining individual components of the PSQI, greater fatigue was moderately correlated with overall self-reported quality of sleep and sleep-related dysfunction, i.e., having trouble staying awake during daytime activities, but showed low correlation with average hours of sleep per night, sleep efficacy (i.e., percent of time in bed spent sleeping), and use of sleep medications. Of note, the HRFS scales demonstrated a low correlation with the ESS, a measure of daytime sleepiness, underscoring the conceptual distinction between "sleepiness" and chronic fatigue. With regard to stress and fatigue, daytime sleepiness and poor nighttime sleep play some part in mediating the relationship between stress and fatigue, but stress appears primarily to be related to HIV-related fatigue via some other mechanism. This intriguing result deserves further scrutiny in future research, as do measures for improving sleep. We are following this cohort for 3 years, and during that time we hope to develop a better understanding of the complex relationships between sleep quality, daytime sleepiness, stressful life events, and HIV-related fatigue. We will be better able to establish the sequence of events as well – to see how changes in one of these variables may be reflected in changes in the others later in the study.

Acknowledgements

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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 non-marijuana 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)

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

[*] Of those reporting any current pain

Table 2

Correlations among HRFS subscales and PSQI subscales

	Fatigue intensity	Overall functional impairment	Impairment in activities of daily living	Impairment in ability to socialize	Impairment in mental functioning
Overall quality of sleep	0.41*	0.42*	0.40*	0.40*	0.40*
Trouble getting to sleep	0.38*	0.32*	0.33*	0.26*	0.32*
Average no. of hours of sleep per night	0.18*	0.22*	0.22*	0.16	0.25*
Average percent time in bed spent asleep	0.24*	0.25*	0.26*	0.24*	0.16
Disturbed sleep	0.40*	0.36*	0.36*	0.36*	0.29*
How often used sleep meds in the past month	0.14	0.13	0.13	0.11	0.11
Sleep-related dysfunction	0.38*	0.46*	0.43*	0.47*	0.42*
Global sleep quality score	0.46*	0.47*	0.46*	0.43*	0.42*

*
$p < 0.05$

Table 3

Multiple regression models of the association between stress, sleep quality, and fatigue

Variable	Fatigue intensity		
	Model 1	Model 2	Model 3
Stress	0.26[*] (0.10, 0.43)	0.26[*] (0.09, 0.43)	0.22[*] (0.06, 0.38)
Daytime sleepiness (ESS)		0.04 (-0.14, 0.23)	0.05 (-0.13, 0.23)
Nighttime sleep quality (PSQI)			0.43[*] (0.27, 0.60)
	Fatigue-related impairment of functioning		
Stress	0.28[*] (0.12, 0.44)	0.26[*] (0.10, 0.42)	0.20[*] (0.05, 0.35)
Daytime sleepiness (ESS)		0.17 (-0.01, 0.35)	0.20[*] (0.03, 0.37)
Nighttime sleep quality (PSQI)			0.44[*] (0.29, 0.59)

All models additionally adjust for monthly income, years since HIV diagnosis, CD4 count, HIV RNA viral load, and ART status.

ESS=Epworth Sleepiness Scale; PSQI=Pittsburgh Sleep Quality Index.

Results are reported as standardized regression coefficient or beta (95% confidence interval).

[*]
$p < 0.05$