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Physiological and Psychological Correlates of Fatigue in HIV Disease

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Fatigue is a frequent symptom reported by persons living with HIV disease and one that affects all aspects of quality of life. To improve quality of care of persons with HIV disease, it is important to address all factors that contribute to fatigue. The purpose of this study was to determine the associations of physiological, psychological, and sociological factors with fatigue in an HIV-infected population. With Piper's integrated fatigue model guiding selection, factors examined in this study were hemoglobin, hematocrit, CD4+ cell count, HIV-RNA viral load, total sleep time, sleep quality, daytime sleepiness, HIV-related symptoms, anxiety, depression, and perceived stress. The sample (N = 79) for this descriptive correlational study was recruited from a primary health care association in South Carolina and consisted of 42 (53.2%) HIV-infected women and 37 (46.8%) HIV-infected men between the ages of 24 and 63 years ($\bar{x}$ = 39.9, s = 7.9). Of the participants, 70 (90%) were African American, 5 (6%) were Caucasian, and 3 (4%) were Hispanic. Using Pearson's r, significant relationships were observed between fatigue and sleep quality, daytime sleepiness, HIV-related symptoms, state anxiety, trait anxiety, depression, and perceived stress. Sleep quality ($F_{5,65}$ = 12.02, P = 0.0009), state anxiety ($F_{5,65}$ = 8.28, P = 0.0054), HIV-related symptoms ($F_{5,65}$ = 4.87, P = 0.0308), and depression ($F_{5,65}$ = 7.31, P = 0.0087) retained significance in a 3-step, backward stepwise elimination model and accounted for 67% of the variance in fatigue. These findings underscore the need for addressing psychosocial stressors and sleep quality in developing effective care for HIV-infected individuals who experience fatigue.

Key words: *sleep, anxiety, perceived stress, depression, HIV, fatigue*

Fatigue, one of the most prevalent and distressful symptoms of HIV infection (Barroso and Lynn 2002), affects all aspects of an individual's life. A multitude

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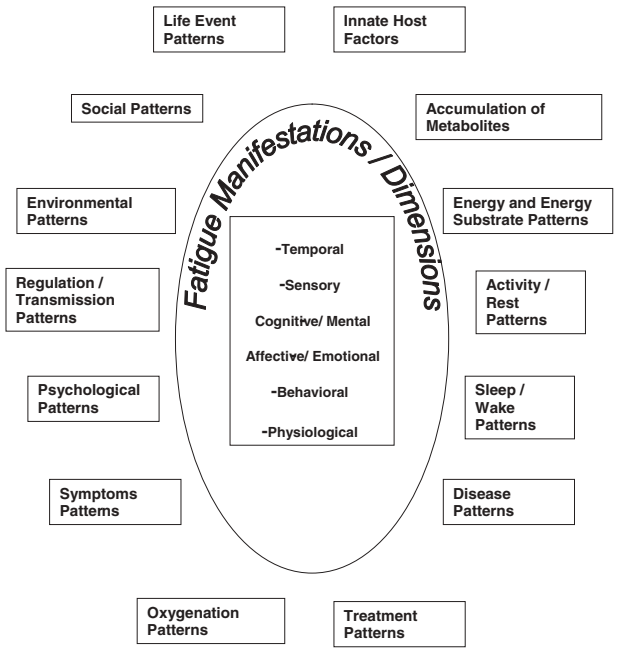

Figure 1. Piper's integrated fatigue model.

of factors may contribute to the fatigue experienced by an HIV-infected individual. Understanding correlates of fatigue allows nurses to plan and provide the holistic care that is most appropriate for an HIV-infected individual who is experiencing fatigue. The purpose of this study was to determine the physiological, psychological, and sociological correlates of HIV-related fatigue.

Theoretical Framework

Piper's integrated fatigue model guided the selection of variables that were examined in this study (Piper and others 1987; Piper 1989; see Fig. 1). Piper has proposed that fatigue has temporal, sensory, cognitive/mental, affective/emotional, behavioral, and physiological dimensions and that it may arise from physiological, psychological, or sociological etiologies. Physiological, psychological, and sociological factors theoretically linked with HIV-related fatigue were examined in the present study.

Background

Fatigue has been defined as "a feeling of tiredness that is influenced by circadian rhythm and occurs on a continuum that has self-perceived energy or vigor at its other end" (Grady and others 1998, p 227). Attributes of fatigue that are often identified include tiredness, lack of energy, exhaustion, lethargy, depression, inability to concentrate, malaise, asthenia, boredom, sleepiness, lack of motivation, and decreased mental status (Winningham and others 1994; Rose and others 1998).

Fatigue is a debilitating symptom that almost always accompanies HIV/AIDS (Darko and others 1992; Hoover and others 1993; O'Dell and others 1996; Rondanelli and others 1997; Breitbart and others 1998; Barroso 1999; Barroso and Lynn 2002; Wollmann and others 2002; Barroso and others 2003) and is sometimes experienced by otherwise asymptomatic HIV-infected individuals (Hoover and others 1993; Enwonwu and others 1996; Grady and others 1998; Newshan and others 2002; Sullivan and others 2003). HIV-infected individuals have identified fatigue as the most distressful symptom they must endure (O'Brien and Pheifer 1993; Nokes and others 1994).

The prevalence of fatigue in HIV disease ranges from 20% to 60% (Longo and others 1990; Darko and others 1992; Hoover and others 1993; Vlahov and others 1994; Breitbart and others 1998; Barroso 1999; Sullivan and others 2003). During the acute phase of the primary infection with HIV, fatigue occurs in most persons. During the asymptomatic phase of the illness, little or no fatigue is experienced. As HIV infection progresses to AIDS, fatigue becomes a persistent, severe symptom (Kaslow and others 1987; Lang and others 1987; Groopman 1998). In a recent study, the most frequently experienced symptoms reported by HIV-infected individuals in an urban outpatient clinic were fatigue, trouble sleeping, anxiety, and pain (Newshan and others 2002).

Although research has focused on the etiology of fatigue associated with HIV infection, the mechanisms have remained elusive. A major obstacle is the inclusion of various populations in the fatigue research. Some researchers have demonstrated a gender difference in fatigue. Women (67%) with AIDS have been found to be more likely to report fatigue than men (49%) with AIDS (Breitbart and others 1998; Sullivan and others 2003). Intravenous drug users (IVDUs) reported more fatigue than homosexual men who were not IVDUs. Female IVDUs reported more fatigue than

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male IVDUs (Breitbart and others 1998). Unsurprisingly, patients older than 35 years reported more fatigue than did younger patients (Singh and others 1997).

Fatigue has been reported in association with opportunistic infections (Cohen and others 1999), the wasting syndrome (Macallan and others 1995), adrenal insufficiency (Piedrola and others 1996), thyroid deficiency (Barroso 1999; Adinolfi 2001b), and hypogonadism (Rabkin and others 2000). HIV-related fatigue is often idiopathic (Carr and others 2000).

Fatigue and Medical Therapy

Fatigue is one of the most commonly reported adverse reactions to antiretroviral medications (Duran and others 2001; McMahon and others 2001; Kessler and others 2002). Fatigue has been identified as a major reason for nonadherence to highly active antiretroviral therapy (HAART; Hagberg and Janson 2001; Molassiotis and others 2002; Monreal and others 2002; Ostrow and others 2002). Reverse transcriptase inhibitors and protease inhibitors are thought to produce fatigue through their toxic effects on skeletal muscle (Molassiotis and others 2002). Fatigue may signal lactic acidosis, a serious and often fatal reaction to nucleoside reverse transcriptase inhibitors (Carr and others 2000; Delgado and others 2001; Anonymous 2002). A number of other approved and investigational drugs, such as interleukin-2, are known to lead to increased fatigue in HIV-infected patients (Grady and others 1998).

Fatigue and Anemia

Anemia is a common complication in persons with HIV disease. Anemia affects approximately 3.4 million Americans and is more common in women and persons living in the South (National Center for Health Statistics 1996). Fatigue is commonly reported by anemic individuals (Moyle 2002) and is a cardinal symptom in the diagnostic criteria for anemia. Profound anemia has serious consequences for HIV-infected individuals in that it has been identified as a prognostic indicator of HIV disease progression and death (Moyle 2002). Although all classifications of anemia are possible in HIV disease and must be differentiated for treatment, the anemia of chronic illness is the most common type of anemia (Phillips and Groër 2002). Anemia adversely affects a range of the dimensions of quality of life, most commonly mediated through fatigue (Moyle 2002).

Clinically, the relationship between anemia and fatigue is well accepted. However, some researchers have been unable to show a clear association. For example, a poor association was found between anemia and fatigue in patients with different types of cancer (Morant 1996), and no correlation was found between anemia and fatigue in patients with advanced breast cancer (Bruera and others 1989). O'Dell and colleagues (1996) found no significant relationships between hemoglobin, hematocrit, albumin, or total protein and fatigue in 20 HIV-positive men and concluded that fatigue is more related to psychosocial factors than to anemia.

Fatigue and Insomnia

Darko and colleagues (1992) found that HIV-infected subjects were more likely to report fatigue than were noninfected subjects, and the HIV-infected subjects were more likely to sleep longer and take more naps. Lee and others (1999) examined the relationship of fatigue to sleep and activity patterns in HIV disease. When compared to women with low fatigue levels, women with high fatigue levels reported more difficulty falling asleep, more awakening from nighttime sleep, poorer daytime functioning, and a higher frequency of depressive symptoms.

Fatigue and CD4+ Cell Count

Contradictory findings have been reported regarding the relationship between CD4+ cell count and fatigue. Some researchers have reported a significant inverse relationship between CD4+ cell count and fatigue (Darko and others 1992; O'Dell and others 1996; Walker and others 1997; Justice and others 1999); however, other researchers have found no relationship between CD4+ cell count and fatigue (de Boer and others 1993; Perkins and others 1995; Breitbart and others 1998; Barroso and others 2003; Sullivan and others 2003). Lee and colleagues (1999) reported significant inverse relationships between CD4+ cell count and evening and morning fatigue in a sample of HIV-infected women.

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Fatigue and HIV-RNA Viral Load

The relationship between HIV-RNA viral load and fatigue remains uncertain. Lavreys and colleagues (2002) examined the relationship between viral load and the constitutional symptoms of primary HIV infection prior to seroconversion and reported a significant relationship between HIV-RNA viral load and fatigue in that population. Other researchers have found no relationship between fatigue and HIV-RNA viral load (Ferrando and others 1998; Barroso and others 2003; Sullivan and others 2003).

Fatigue and Anxiety

Anxiety is a recognized correlate of fatigue in HIV/AIDS (Groopman 1998). In a study of anxiety syndromes and symptoms in 173 homosexual men with AIDS, Sewell and colleagues (2000) found a positive relationship between anxiety and fatigue. Other researchers have reported similar relationships between anxiety and fatigue in HIV disease (Barroso and others 2003).

Fatigue and Depression

Fatigue, depression, and weight loss are commonly reported by HIV-infected individuals (Perkins and others 1995). Health care providers may incorrectly attribute these symptoms to disease progression and fail to recognize their patients' underlying depression. Unfortunately, it is difficult to sort out the relationship between fatigue and depression (Walker and others 1997). Instruments used to measure depression commonly include somatic complaints/symptoms that are similar to symptoms of fatigue. In addition, it is recognized that fatigue is a major symptom of depression.

Significant relationships between depression and fatigue have been reported in samples of HIV-positive individuals (Perkins and others 1995; Walker and others 1997; Breitbart and others 1998; Barroso and others 2003). However, some researchers suggest that fatigue in HIV-positive individuals may be a symptom of underlying depression, whereas others suggest that it is a physical symptom independent of mood. Ferrando and colleagues (1998) investigated the prevalence of fatigue in HIV illness and whether fatigue, being associated with depression, independently affects physical functioning and disability. These authors concluded that although fatigue is associated with depression, it does not seem to be merely a symptom of depression. They also concluded that fatigue independently contributes to physical limitations and disability and should therefore be independently assessed and treated. On the other hand, other studies have suggested that fatigue is a manifestation of depression in HIV illness (Perkins and others 1995; Lyketsos and others 1996). Perkins and colleagues (1995) found that depressive symptoms and major depression were predictors of fatigue severity. In addition, Lyketsos and colleagues (1996) found that fatigue and depressive symptoms were closely associated across stages of HIV illness and concluded that fatigue is most likely a symptom of depression. Other researchers found a close association between somatic symptoms of depression and the number of AIDS-related diagnoses. Almost 50% of their sample reported depressive symptoms, and more than two-thirds of the subjects reported fatigue (Kalichman and others 1995). Therefore, the authors concluded that the assessment of depression in individuals with HIV-related symptoms should include only instruments without somatic symptoms.

Fatigue and Perceived Stress

Using the Global Fatigue Index as a measure of fatigue, Bormann and others (2001) reported a significant direct correlation between perceived stress and fatigue in a sample of HIV-infected individuals. Breitbart and others (1998) found that HIV-infected patients with fatigue report a greater degree of overall psychological distress.

Fatigue and Quality of Life

Fatigue is strongly related to quality of life (Darko and others 1992; Cleary and others 1993; Winningham and others 1994; Darko, Mitler, and others 1995; Yellen and others 1997; Breitbart and others 1998; Cunningham and others 1998; Groopman 1998; Eller 2001). Fatigue can disrupt normal activities of daily living (Winningham and others 1994), reduce physical functioning (Winningham and others 1994; Wilson and Cleary 1996; Fleishman and Crystal 1998), and reduce self-care activities (Hart and others

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1990; Rhodes and others 1988). Fatigue affects HIV-infected individuals' ability to work and to take care of themselves and their families, their physical and emotional well-being, their enjoyment of life, and their ability to be intimate with their partners (Groopman 1998). Fatigue may be the most important symptom in an HIV-infected individual's decision to discontinue employment, and with that decision comes loss of income and loss of health insurance (Darko and others 1992).

Summary

Although other researchers have demonstrated significant relationships between these physiological and psychological factors and fatigue, no report was found in which all these variables were tested in a single model. Understanding the variables that best predict fatigue in HIV-infected individuals will allow health care practitioners to develop plans of care that focus on factors related to fatigue in HIV disease.

Method

Design

The data reported in this article were collected as part of a study designed to examine physiological and psychological correlates of fatigue in HIV disease. A descriptive correlational design was used.

Sample

The sample for this report was recruited from a primary health care association in Columbia, South Carolina. The sample consisted of 79 women and men documented to be HIV infected. Individuals who were 18 years of age or older, able to read and understand English at a 6th-grade level, and receiving health care services at the primary health care association were included in the study. No one was excluded on the basis of gender or ethnicity.

Procedure

The Office for Research Protection at the University of South Carolina approved the study and its procedures prior to any data collection. Physicians at the community health center referred potential participants to the study. Female research assistants who were specially trained to provide full information regarding the research study and who signed a confidentiality statement collected all data. Participants were accessed at the time of their medical appointments for periodic physical examinations and laboratory studies. A nurse directed individuals who were interested in the study to a large, comfortable conference room in the same building. The conference room provided comfort, privacy, and easy access to the participants. After receiving an informed consent statement and being fully informed of the nature and duration of the study by the research assistant, individuals who agreed to participate were asked to read and sign the informed consent statement. In addition, they were asked to sign a consent form that gave the primary health care practice permission to release the results of their laboratory studies (complete blood count, HIV-RNA viral load, and T helper cell [CD4+]) count to the researchers.

Data were collected using a structured questionnaire, which was completed on the same day the blood for laboratory tests was drawn. The research assistant was available to answer any questions the participants might have about the study. After the participants completed the questionnaire, the research assistant placed a wrist actigraph on their nondominant arms and instructed them in the care of the wrist actigraph. Participants were asked to wear the wrist actigraph continually for 3 days and nights. Participants and the research assistants arranged an appointment to return the wrist actigraphs. When they returned the wrist actigraphs, the participants were paid $20 for taking part in the study.

Instruments

Demographic data form. Participants were asked to report standard demographic variables such as age and race and HIV-related variables such as route of infection, stage of illness, symptoms, antiretroviral medications, and hematinic medications (particularly erythropoietin and iron).

Revised Piper Fatigue Scale (RPFS). The RPFS was used to measure subjective fatigue. The RPFS consists of 22 items that are numerically scaled from 0 (*no fatigue*) to 10 (*high fatigue*), and there are 5 items

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that give additional clinical information but are not used in the scoring of fatigue. The RPFS yields a total fatigue score and 4 subscale scores that reflect the behavior/severity, affective meaning, sensory, and cognitive/mood dimensions of fatigue (Piper 1989). The 22 numerically scaled items are summed to give the total fatigue score that was used in this study to measure subjective fatigue. The total fatigue score is divided by 22 to give a fatigue score that ranges from 0 to 10 (0 = *no fatigue*, 1 to 3 = *mild fatigue*, 4 to 6 = *moderate fatigue*, and 7 to 10 = *severe fatigue*). The RPFS demonstrates internal consistency with a Cronbach's α of 0.97. A higher score indicates greater subjective fatigue (Piper and others 1998).

Hemoglobin, hematocrit, HIV-RNA viral load, and CD4+ cell count. The results of the physiological variables were recorded directly from each individual's medical record. Hemoglobin and hematocrit were used to measure the degree of anemia. HIV-RNA viral load was measured using reverse transcriptase polymerase chain reaction.

Wrist actigraph. A MiniMotionLogger wrist actigraph (ambulatory monitoring) was used to measure total sleep time. The wrist actigraph is a small device about the size of a quarter that was attached to each participant's nondominant arm. The wrist actigraph detects motion, which is converted to an electric signal by a piezoelectric crystal. Data from the wrist actigraph are downloaded into a microcomputer for analysis. An algorithm converts the signal into periods of sleep and activity. The wrist actigraph allows the estimation of the following parameters: (1) sleep-onset latency, (2) wakening after sleep onset, (3) sleep duration, (4) percentage sleep, and (f) total sleep time. Significant correlations have been reported between polysomnography and the measurements of the wrist actigraph on sleep-onset latency ($r = 0.70$, $P < 0.0001$), wake after sleep onset, ($r = 0.25$, $P < 0.0001$), sleep duration, ($r = 0.89$, $P < 0.0001$), and total sleep period ($r = 0.90$, $P < 0.0001$; Cole and others 1992). These significant correlations support the validity of this instrument to measure total sleep time. Total sleep time was used as the measure of sleep activity.

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-report instrument that measures subjective sleep quality. This instrument contains 19 self-report items. The instrument yields a total sleep quality score and 7 component scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). The total sleep quality score was used to measure sleep quality. The total sleep quality score has a reported internal consistency of 0.83 and a test-retest reliability of 0.85. Validity of the PSQI is supported by its ability to discriminate controls from depressives and individuals with diagnosed sleep disorders. The findings of the PSQI are supported by concurrent polysomnography. Possible scores for the total sleep quality scale range from 0 to 21. "A PSQI global score greater than 5 indicates severe difficulties in at least 3 areas, or moderate difficulties in more than 3 areas" (Buysse and others 1989). A higher score indicates poorer sleep quality (Buysse and others 1991).

Epworth Daytime Sleepiness Scale (ESS). The total score for the ESS was used to measure daytime sleepiness. This scale asks individuals to rate on a scale of 0 to 3 how likely they are to doze off or fall asleep in 8 specific situations. The total score for the ESS has a reported reliability of 0.83 and a test-retest reliability of 0.88 for patients. Possible scores can range from 0 to 24. A higher score indicates greater daytime sleepiness (Johns 1991).

HIV-Related Symptom Scale (HSS). The HSS was used to measure the frequency of HIV-related symptoms. This instrument is composed of 19 symptoms (e.g., diarrhea, fever, weight loss, white patches in the mouth) that are commonly experienced by HIV-infected individuals. The HSS asked participants to rate on a scale of 1 (*no problem*) to 4 (*very much of a problem*) how much of a problem each of the symptoms had been for them during the past month. Two of the symptoms on the HSS were fatigue and weakness. These symptoms were not included in the total score for these analyses because the outcome measure was fatigue. The responses for each of the remaining 17 items were summed to give a total HIV-related symptom score. A higher score indicated that an individual was experiencing greater frequency of HIV-related symptoms. Reliability was supported in this sample with a Cronbach's α of 0.87.

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Table 1. Description of the Instruments Used

Instrument	$\bar{x}$[a]	*s*	Potential Range	Actual Range	α
Piper Fatigue Scale	3.9	2.8	0–10	0–9.9	0.98
Hemoglobin (mg/dL)	12.9	1.7	NA	7.8–16.0	NA
Hematocrit (%)	38.3	4.9	NA	24.0–47.7	NA
CD4+ cell count (cells/mm^3)	412	268	NA	8–1140	NA
HIV-RNA viral load	38,577	83,621	NA	0–516,000	NA
Total sleep time (min)[b]	399.3	168.3	NA	119.7–966.7	NA
Pittsburgh Sleep Quality Index	12.3	3.9	0–21	5–21	0.77
Epworth Daytime Sleepiness Scale	8.4	5.9	0–24	0–22	0.84
HIV Symptom Distress Scale	26.2	8.6	17–68	17–50	0.87
Spielberger's State Anxiety Inventory	40.9	13.6	20–80	20–78	0.92
Spielberger's Trait Anxiety Inventory	45.2	11.4	20–80	20–74	0.91
Center for Epidemiological Studies–Depression	22.3	11.3	0–60	1–47	0.87
Perceived Stress Scale	68.0	19.2	0–120	2–114	0.95

a. The mean, standard deviation, actual range, and α reported are from the present study.
b. Total sleep time obtained via wrist actigraph.

Spielberger's State-Trait Anxiety Inventory (STAI). The STAI is a 40-item Likert-type instrument used to measure state anxiety (transitory) and trait anxiety (relatively stable anxiety proneness). There are 20 items for the state anxiety scale and 20 items for the trait anxiety scale. The participants were asked to respond to each of the items on a 4-point scale ranging from 1 (*not at all*) to 4 (*very much so*). The state anxiety scale has reported test-retest reliabilities ranging from 0.16 to 0.92 and internal consistencies ranging from 0.83 to 0.92. The trait anxiety scale has reported test-retest reliabilities ranging from 0.73 to 0.92 and internal consistencies ranging from 0.86 to 0.92. Construct and concurrent validity of the STAI have been supported in numerous studies. A higher score indicates greater anxiety (Spielberger and others 1971).

Center for Epidemiological Studies Depression Scale (CES-D). The CES-D is a 4-point, 20-item scale that measures depressive symptoms. The participants were asked to rate how often they had experienced the depressive symptom represented by each of the 20 items in the past week. Responses range from 0 (*not at all to 1 day per week*), 1 (*1 to 2 days per week*), 2 (*3 to 4 days per week*), to 3 (*5 to 7 days per week*). Possible scores for the total scale range from 0 to 60. Reported internal consistencies for the instrument have ranged from 0.83 to 0.90. Concurrent and construct validity have been supported in a number of studies. A higher score indicates greater depressive symptoms (Radloff 1977). A cutoff point of greater than 16 is widely accepted as diagnostic of clinical depression (Radloff 1977; Parikh and others 1988; Beekman and others 1997; Houston and others 2001, 2002).

Perceived Stress Scale (PSS). The PSS is a 30-item instrument that measures perceived stress (Levenstein and others 1993). The instrument yields a total score for perceived stress and 7 subscale scores. The instrument can be administered to collect data about general perceived stress (in the past year or two) or recent perceived stress (in the past month). In this study, the participants were asked to consider the past month and to rate each of the items on a scale of 1 (*almost never*) to 4 (*usually*). The instrument has a reported test-retest reliability of 0.82 for the General Form, but the Recent Form varied by a mean factor of 1.9 over 6 months. Reported internal consistencies were greater than 0.90 for both forms of the PSS. The developers of the PSS have reported concurrent and construct validity. The total score was used to measure perceived stress in this study. A higher score indicates greater perceived stress (Levenstein and others 1993). The psychometric properties of the instruments used in this study are summarized in Table 1.

Data Analysis

The data were entered by a research assistant and verified by an independent observer. Frequencies and

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Table 2. Description of Fatigue Based on the Demographic Characteristics of the Sample

Characteristic	Frequency	%	$\bar{x}$ Fatigue	*s*
Gender				
Female	42	46.8	3.8	2.8
Male	37	53.2	4.1	2.8
Race				
African American	70	89.8	3.8	2.8
Caucasian	5	6.4	4.5	3.0
Hispanic	3	3.8	4.6	0.9
Missing	1			
Partnership status				
Single	64	82.1	3.8	2.9
Partnered or married	14	17.9	4.7	2.1
Missing	1			
Stage of illness				
Asymptomatic	13	23.2	3.0	3.0
Symptomatic	25	44.6	3.6	2.6
AIDS	18	32.2	3.7	2.7
Missing	23			
Antiretroviral therapy				
Yes	52	68.4	3.8	2.6
No	24	31.6	4.2	3.3
Missing	3			
Fatigue				
None (0)	17	22.1	0.2	0.3
Mild (1–3)	22	28.6	2.7	0.9
Moderate (4–6)	27	35.1	5.4	0.9
Severe (7–10)	11	14.3	8.4	0.9
Missing	2			

NOTE: The revised Piper Fatigue Scale was used to obtain measures of subjective fatigue.

percentages were calculated for each of the sociodemographic variables. Reliabilities for each of the research instruments were estimated using Cronbach's α reliability coefficient. Bivariate correlations were calculated between fatigue and the theoretically selected variables. A P value < 0.05 was established as the level of statistical significance for the backward stepwise elimination model. Variables that were significantly related to fatigue in the bivariate correlations were entered into a backward stepwise elimination model. Collinearity diagnostics were performed for the variables in the full model. Statistical power for the backward stepwise regression was calculated to be 0.80 with a medium effect size in this sample.

Results

All participants in this study were infected with HIV. They were predominately African Americans ($n = 70$), and 5 were Caucasian and 3 Hispanic. Forty-two participants were women, and 37 were men. The majority of the participants were single ($n = 64$). The remaining 14 participants reported that they were partnered. The participants ranged in age from 24 to 63 years ($\bar{x} = 39.9$, $s = 7.8$). Thirteen participants were asymptomatic, 25 were symptomatic, and 18 had developed AIDS. The frequencies do not add to 79 in all cases due to missing data points. Means, standard deviations, and missing data points are reported in Table 2.

Fifty-two participants were receiving combination antiretroviral therapy, and 24 (31.6%) were not receiving any antiretroviral therapy. An independent t test was performed to test whether there was a difference in the total fatigue scale between participants who were receiving combination antiretroviral therapy and those participants who were not taking any antiretroviral medications. No significant difference was detected ($t = 0.50$, $P = 0.62$).

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Comorbidity was examined in this sample. Ten subjects reported being treated for hypertension; 9 were treated for depression; 8 were treated for gastroesophageal reflux disease; 5 participants were treated for diabetes mellitus, all of whom received oral hypoglycemics and 2 of whom received insulin; 2 were being treated for dyslipidemia; 3 were receiving appetite stimulants; 25% of the sample was anemic, with 8 men (21.6%) having a hemoglobin count less than 14 g/dL and 12 women (28.6%) having a hemoglobin count less than 12 g/dL, thus meeting the criteria for anemia. Two participants reported taking erythropoietin, 5 participants took iron supplements, and 15 participants reported taking multiple vitamins.

Depression scores for this sample ranged from 1 to 47, with a mean of 22.3 ± 11.3. In this sample, 54 participants (68.4%) scored greater than 16 on the CES-D, which is consistent with clinical depression. There was no gender difference in depression scores (independent *t* test; $t = 1.54$, $P = 0.13$).

Description of Fatigue

In our sample of 79 HIV-infected men and women, we found that 60 participants (77.9%) reported some degree of fatigue, with 22 (28.6%) reporting mild fatigue, 27 reporting moderate fatigue (35.1%), and 11 (14.3%) reporting severe fatigue (see Table 2).

No differences in total fatigue were observed between men and women (independent *t* test; $t = 0.50$, $P = 0.62$). Likewise, no significant differences were observed in the total fatigue score between participants who were asymptomatic, symptomatic, or who had progressed to AIDS (ANOVA; $F_{2,52} = 0.28$, $P = 0.75$). Finally, no significant differences in fatigue were observed between those who were taking protease inhibitors and those who were not taking protease inhibitors (independent *t* test, $t = 0.78$, $P = 0.45$). (Refer to Table 2 for means and standard deviations.)

Bivariate Correlations

Relationships of the demographic variables with total fatigue were tested using Pearson's coefficient of correlation (Pearson's *r*). No significant relationship was found between age and total fatigue (Pearson's correlation coefficient; $r = -0.19$, $P = 0.17$). Significant relationships were observed between fatigue and sleep quality ($r = 0.53$, $P < 0.0001$), daytime sleepiness ($r = 0.33$, $P = 0.0039$), HIV-related symptoms ($r = 0.61$, $P < 0.0001$), state anxiety ($r = 0.71$, $P < 0.0001$), trait anxiety ($r = 0.57$, $P <. 0.0001$), depression ($r = 0.65$, $P < 0.0001$), and perceived stress ($r = 0.71$, $P < 0.0001$), as shown in Table 3.

Tests for Multiple Collinearity

Because multicollinearity issues are of concern when multiple psychometric measurements are used in regression analyses, collinearity diagnostics were performed for each of the variables in the full model. All variance inflation factors were <10, and the condition inflation factors were <30, indicating that multicollinearity was not a problem for this model.

Backward Stepwise Elimination

Subsequently, independent variables (sleep quality, daytime sleepiness, HIV-related symptoms, state anxiety, trait anxiety, depression, and perceived stress) that demonstrated a significant association with the dependent variable (fatigue) were entered into a backward stepwise elimination equation. In a 3-step solution, trait anxiety and perceived stress fell out of the model. Sleep quality, state anxiety, HIV-related symptoms, and depression retained statistical significance and explained 67% of the variance in fatigue, as shown in Table 4.

Discussion

The results from the present study indicate a high prevalence of fatigue in a predominantly African American population of HIV-infected individuals. Our findings regarding the high prevalence of fatigue in this sample of HIV-infected men and women are consistent with those of previous researchers (Darko and others 1992; Hoover and others 1993; O'Dell and others 1996; Rondanelli and others 1997; Breitbart and others 1998; Barroso 1999; Barroso and Lynn 2002; Wollmann and others 2002; Barroso and others 2003).

We found no significant relationships between fatigue and gender, race, partnership status, or antiretroviral therapy. The failure to find a gender difference in fatigue in HIV-infected individuals is incon-

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Table 3. Bivariate Correlations among the Study Correlations Using Pearson's *r* (*n* = 77)

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. Fatigue[a]												
2. Hemoglobin	0.030											
3. Hematocrit	0.001	0.977****										
4. CD4+ cells	0.057	0.414**	0.450***									
5. Viral load	0.249	–0.178	–0.166	–0.259								
6. Total sleep time[b]	–0.084	–0.232	0.243	–0.175	0.335*							
7. Sleep quality[c]	0.526****	–0.041	0.053	0.051	–0.028	–0.182						
8. Daytime sleepiness[d]	0.333**	0.149	0.093	–0.269	–0.023	–0.072	0.186					
9. Symptoms[e]	0.551****	–0.258*	–0.320*	–0.194	0.133	0.030	0.287*	0.335**				
10. State anxiety[f]	0.706****	0.004	0.013	–0.056	0.209	–0.097	0.423****	0.175	0.515****			
11. Trait anxiety[g]	0.568****	0.076	0.043	0.005	0.107	–0.133	0.251*	0.221	0.475****	0.744****		
12. Depression[h]	0.645****	0.188	0.152	–0.062	0.208	–0.110	0.297**	0.366**	0.492****	0.678****	0.780****	
13. Perceived stress[i]	0.712****	0.077	0.056	–0.068	0.163	–0.028	0.411***	0.343**	0.543****	0.772****	0.801****	0.803****

a. Revised Piper Fatigue Scale (total score).
b. Wrist actigraph.
c. Pittsburgh Sleep Quality Index (total score).
d. Epworth Daytime Sleepiness Scale.
e. HIV Symptom Distress Scale.
f. Spielberger's State Anxiety Inventory.
g. Spielberger's Trait Anxiety Inventory.
h. Center for Epidemiological Studies–Depression Scale.
i. Perceived Stress Scale.
*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$. ****$P < 0.0001$.

sistent with the findings of Breitbart and colleagues (1998) and Sullivan and colleagues (2003). This may be explained in part by the different methods that were used in data collection. Sullivan and colleagues collected data via retrospective chart reviews and included only individuals who reported fatigue as the primary reason for a health care visit, fatigue on more than one health care visit, or fatigue that limited the patient in his or her employment or sport. Likewise, the researchers acknowledged use of an instrument that has a less sensitive case definition for fatigue than the one we used. Breitbart and colleagues (1998) collected their data to the advent of HAART, more of the participants had progressed to AIDS, and they used a dichotomous item to measure the presence of fatigue. It is likely that the total score for the Piper Fatigue Scale is a more sensitive measure of fatigue.

There were a number of physiological and psychological characteristics associated with self-reported fatigue in the subject group. However, the highest correlations with fatigue were found among psychological variables. A backward stepwise regression emphasized the impact of both psychological and physiological characteristics, as both types of variables were included in the model that was predictive of fatigue in the subjects.

Table 4. Backward Stepwise Regression Analysis Summary for Variables Predicting Fatigue

Variable	β	Standard Error β	*F*	*P*
Intercept	–4.23	0.84	25.2	< 0.0001
Sleep quality	0.20	0.06	12.0	0.0016
State anxiety	0.06	0.03	8.3	0.0054
HIV-related symptoms	0.06	0.02	4.9	0.0308
Depression	0.07	0.03	7.3	0.0087

NOTE: $R^2 = 0.67$; Model $F_{5,65} = 31.66$, $P < 0.0001$; $N = 71$.

Fatigue is the most common clinical complaint of HIV-infected individuals, with a prevalence range of

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10% to 30% among asymptomatic patients and 40% to 50% among AIDS patients (Adinolfi 2001a, 2001b; Sullivan and others 2003). Although fatigue is associated with deteriorating physical health, mental well-being, and quality of life, it is also predictive of diminishing physical function (Ferrando and others 1998). Fatigue affects the HIV-infected individual financially, as it generally leads to decreased vigor, lower quality of work, and increased absenteeism (Darko and others 1992; Darko, Mitler, and others 1998).

Although fatigue has a clear impact on the overall quality of life of a large number of HIV-infected individuals, it is difficult to define and measure. Therefore, the physiological and psychological characteristics responsible for feelings of fatigue have been elusive. Finding the causes of fatigue is difficult because of the likelihood that fatigue associated with HIV infection is the result of a number of pathological conditions that are constantly in flux. Not surprisingly, there is a significant amount of conflicting data concerning the relationships between fatigue and physiological and psychological characteristics. For example, there are conflicting reports of the association between fatigue and CD4+ cell count. One study found an inverse relationship between level of fatigue and CD4+ count in HIV-infected gay men (Walker and others 1997). These authors suggest that this relationship may be caused by exhaustion of the body from fighting infection during advanced stages of HIV. On the other hand, 3 other studies found no relationship between the 2 variables (Ferrando and others 1998; Barroso and Lynn 2002; Sullivan and others 2003). Our findings are in support of studies showing no correlations between measures of immune function and reported symptoms of HIV illness (Rabkin and others 1991; Perry and others 1992; de Boer and others 1993; Perkins and others 1995; Breitbart and others 1998; Ferrando and others 1998; Barroso and others 2002; Sullivan and others 2003).

One interesting outcome of the present study is the very low prevalence of anemia in the subject group. Anemia is a common physiological disturbance in HIV infection, with up to 80% of the population experiencing anemia at some point (Doweiko and Groopman 1998). Fatigue is arguably the most common presenting symptom associated with anemia. The anemic condition results from a number of mechanisms including disrupted hematopoiesis, bone marrow infection, hemolysis, and antiviral therapy (Groopman 1998). Unfortunately, although significant technological discoveries have advanced HIV treatment, there has been little change in the prevalence of anemia in the HIV-infected population (Mocroft and others 1999). In the present study, only a relatively small portion of the subjects, about 25%, presented with anemia. This disproportionately low number could be due to a number of factors. First, the incidence of anemia rises along with the number of symptoms and as the individual reaches AIDS status. Our participant group consisted of primarily asymptomatic ambulatory individuals. Second, the anemia associated with HIV infection may be due to nutritional deficiencies (Doweiko and Groopman 1998). Since our subjects were recruited at a highly recognized primary care facility with a specialization in HIV infection, it is likely that the individuals' conditions, including nutritional status, were well managed.

With a range of 5 to 21 on the PSQI, all subjects in our study reported pathological sleep disturbances. Our data indicate that the subjects averaged approximately 6.7 ± 2.8 h of sleep per night. Although there was a wide range of total sleep time and the average appears to be in the low range, there was no correlation between total sleep time and fatigue. However, both sleep quality and daytime sleepiness were correlates of fatigue. Furthermore, backward stepwise regression analysis indicates that sleep quality is 1 of the 4 determinants of fatigue in our subject population. These findings would suggest that the feelings of fatigue associated with HIV infection in our group are likely due to altered sleep patterns rather than hours of sleep. This possibility is supported by research from Darko and associates (Darko, Miller, and others 1995; Darko, Mitler, and others 1995; Darko and others 1998) indicating HIV-dependent changes in nocturnal secretion of specific hormones that might contribute to sleep pathologies other than insomnia. These hormonal changes included plasma levels of tumor necrosis factor–α and growth hormone, both of which have been linked to sleep patterns and resulting sleep quality. A relationship has further been shown between morning fatigue and measures related to sleep quality, including duration of wake episodes during the night, napping, and perception of sleep disturbance during the past week. In addition, the number of awakenings throughout the night predicted the severity of fatigue,

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and lower CD4+ cell counts were related to greater daytime sleep and higher morning and evening fatigue (Lee and others 1999). Thus, it appears that certain physiological alterations observed in HIV illness contribute to altered sleep patterns that could result in feelings of fatigue during the day.

Physical symptoms of HIV infection also affect sleep variables and showed a relatively high correlation with fatigue in our study. Our subjects reported an average score of 30.8 ± 10.2 (range = 17–58) out of a possible 68 on the HSS. Many of these physical symptoms, such as pain, have been shown to contribute to fatigue in the HIV-infected individual (Breitbart and others 1998). Symptoms of HIV were included in the regression model for determinants of fatigue in this population of infected subjects. Very few studies have been done using the HSS since it was recently developed. However, the items on the scale are valid; the Cronbach's α for the entire tool was 0.94.

Psychological factors have been proposed as the primary mechanism for fatigue in HIV-positive individuals. In a study examining the relationship between fatigue and physiological parameters, no significant associations were found between hematocrit, hemoglobin, total protein, and albumin. The authors concluded that there is a stronger association between fatigue and psychological parameters than between fatigue and physiological parameters (O'Dell and others 1996).

We found that a majority of the participants in our study scored greater than 16 on the CES-D, which indicates a high prevalence of clinical depression in this sample. Some studies examining the prevalence of depression in HIV patients reporting fatigue have not supported the hypothesis that HIV-related fatigue is associated with depression (Walker and others 1997; Breitbart and others 1998). In our study, depression and fatigue showed a relatively high correlation. Depression retained significance in the final backward stepwise elimination model. We support the notion that the level of depression is associated with the number of symptoms resulting from HIV infection. The correlation between depression and fatigue may therefore be dependent on the HIV-related symptoms that partially determine fatigue.

In the present study, both state and trait anxiety correlated with fatigue. Furthermore, state anxiety survived the backward stepwise regression analysis and was included in the model of determinants of fatigue. The significant relationships found between state anxiety, trait anxiety, and fatigue are consistent with findings of prior research (Sewell and others 2000; Barroso and others 2003). Interestingly, both state and trait anxiety correlated with sleep quality and HIV-related symptoms. Further investigation will be required to determine the relationship between anxiety, sleep, and symptoms. However, since sleep quality is partially dependent on the degree of physical limitation (Gielen and others 2001) and on the individual's level of psychological distress (Breitbart and others 1998), to suggest a cyclical interaction of those 3 characteristics that results in fatigue would not be too speculative. This suggestion is supported by a study of anxiety syndromes and symptoms in 173 homosexual men with AIDS demonstrating a positive relationship between anxiety and fatigue (Sewell and others 2000).

In the present study, perceived stress was highly correlated with fatigue; however, perceived stress did not hold up in the final regression model when the other variables were taken into account. Further research is needed to determine whether the relationship between perceived stress and fatigue may be mediated by other factors. Perceived stress is not typically examined in fatigue research. Breitbart and others (1998) found that HIV-infected patients with fatigue report a greater degree of overall psychological distress, and a number of studies have shown a higher level of the stress hormone cortisol in the plasma of HIV-infected individuals as compared to HIV-negative subjects (Clerici and others 1997). It is well established that increased unpredictability in a situation will increase perceived stress and cortisol levels (Malarkey and others 1995; Steptoe and others 1998; Atanackovic and others 2002). It follows that an individual with a diagnosed HIV infection would have enhanced stress reactivity to other stressors; in fact, hypercortisolemia is characteristic in the asymptomatic stages of HIV infection. The increased levels of cortisol are related to increased arousal, decreased sleep, and reduced rapid eye movement sleep (Born and others 1986). Cortisol enhances HIV replication as well (Markham and others 1986). Therefore, the association of perceived stress and fatigue may be mediated by stress-hormone-related sleep-quality disruption and other factors related to increased viral load.

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Study Limitations

Although this study presents very useful information, some limitations should be noted. First, the participants for this study were recruited from 1 medical practice in 1 geographic region, the southeastern United States. The physicians in that medical practice referred patients who met the study criteria to the research study. Using this convenience sample may have resulted in bias through self-selection. The generalizability of the findings of this study is further limited in that the sample was predominantly composed of 1 racial group, African Americans. And finally, fatigue may be influenced by a number of sociodemographic factors that were not collected as part of this study.

Clinical Implications

Fatigue is underreported by patients and undertreated by health care providers (Justice and others 1999; Adinolfi 2001b; Curt and Johnston 2003). A reason may be that HIV-infected patients and their health care providers may not be giving adequate attention to the symptom of fatigue (Groopman 1998). Health care providers should reconsider whether their communication skills are facilitative and should question HIV-infected patients about all bothersome symptoms, such as fatigue, at each visit (Eller 2001). Health care providers should also reassess their perception of fatigue and their approach to treating fatigue (Groopman 1998).

Thorough assessment of fatigue is the basis for planning effective interventions for HIV-related fatigue. That assessment should include its onset, duration, severity, factors that increase and decrease the level of fatigue, self-care interventions tried by the patient, and the resolution of fatigue. Based on the findings of our study, a thorough psychosocial assessment is beneficial in helping the fatigued patient. A plan of care that considers the whole patient (physiologic factors, roles and responsibilities of the patient, support systems, and factors such as depression and anxiety) is necessary to help the patient achieve an optimum level of health. Fatigue level must be reevaluated at each contact with the patient.

Implications for the Integrated Fatigue Model

Certainly, this study did not address the integrated fatigue model in its entirety. However, the findings of this study do support the multidimensional nature of the fatigue associated with HIV disease and help to establish the need for considering sleep quality, anxiety, HIV-related symptoms, and depression in the care of HIV-infected women and men who are experiencing fatigue.

Implications for Future Research

Although this study provides important information about this sample, the descriptive, correlational design does not allow for causal inference. An important follow-up to this study would be to develop and test an intervention targeting these factors to see if such an intervention would decrease fatigue and improve quality of life for HIV-infected individuals. In a future intervention study, the sample should include a greater percentage of individuals who are anemic and who report significant levels of fatigue. The sample was not adequate to detect fatigue due to anemia. Objective measures of fatigue would provide valuable insight into metabolic causes.

Conclusion

In summary, the present study examined selected physiological and psychological correlates of fatigue. The results indicated that the physiological characteristics of sleep quality, daytime sleepiness, and HIV-related symptoms correlated with fatigue. The psychological characteristics that correlated with fatigue were state and trait anxiety, depression, and perceived stress. A backward stepwise regression model indicated that almost 70% of the variability in fatigue could be explained in a model containing sleep quality, state anxiety, HIV-related symptoms, and depression. These data indicate that the high prevalence of fatigue in the HIV-infected population is a multifactorial syndrome that includes both physiological and psychological correlates. The results also suggest that stress-related factors probably contribute significantly to the fatigue syndrome.

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