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Patterns of Morning and Evening Fatigue Among Adults with HIV/AIDS

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Abstract

Aims and objectives—Describe patterns of morning and evening fatigue in adults with HIV and examine their relationship to demographic and clinical factors and other symptoms.

Background—Most studies of HIV-related fatigue assess average levels of fatigue and do not address its diurnal fluctuations. Patterns of fatigue over the course of the day may have important implications for assessment and treatment.

Design—A cross-sectional, correlational design was used with six repeated measures over 72 hours.

Method—A convenience sample of 318 HIV-infected adults was recruited in San Francisco. Socio-demographic, clinical and symptom data were collected with questionnaires. CD4+ T-cell count and viral load were obtained from medical records. Participants completed a four-item version of the Lee Fatigue Scale each morning and evening for three consecutive days. Participants were grouped based on their diurnal pattern of fatigue (high evening only, high morning only, high morning and evening and low morning and evening). Group comparisons and logistic regression were used to determine the unique predictors of each fatigue pattern.

Results—The high evening fatigue pattern was associated with anxiety and the high morning pattern was associated with anxiety and depression. The morning fatigue pattern showed very little

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fluctuation between morning and evening, the evening pattern showed the largest fluctuation. The high morning and evening pattern was associated with anxiety, depression and sleep disturbance and this group reported the most fatigue-related distress and interference in functioning.

Conclusions—These results provide initial evidence for the importance of assessing the patient's daily pattern of fatigue fluctuation, as different patterns were associated with different symptom experiences and perhaps different etiologies.

Relevance to clinical practice—Different fatigue patterns may benefit from tailored intervention strategies. Management of depressive symptoms could be tested in patients who experience high levels of morning fatigue.

Keywords

Fatigue; HIV/AIDS; Symptom Control; Anxiety; Depression; Quality of Life; nurses; nursing

Introduction

Studies have shown that 37–69% of adults living with HIV experience fatigue (Lee *et al*. 2001, Phillips *et al*. 2004, Henderson *et al*. 2005, Sullivan and Dworkin 2003, Grierson *et al*. 2002). Fatigue can interfere with people's capacity for self care and daily activities (Jenkin *et al*. 2006, Barroso 2001, Harmon *et al*. 2008); therefore, it is important for nurses to understand different types of fatigue so that appropriate intervention strategies can be developed and tested.

Fatigue is a complex multidimensional symptom. It can be defined as a sense of exhaustion, lack of energy, or tiredness distinct from sleepiness, sadness or weakness (Lee *et al*. 1994, Krupp *et al*. 1988, Lerdal 1998). However, unlike typical tiredness, clinically significant fatigue is unrelieved by a night of good quality sleep (Lee *et al*. 1994). Since sleep is normally restorative, individuals generally have more energy in the morning than in the evening. While daily fluctuations in fatigue and energy levels are common (Dimsdale *et al*. 2003), a general pattern of lower fatigue in the morning and higher fatigue in the evening has been reported in a variety of patient populations, including individuals with HIV infection (Lee *et al*. 1999, Barroso 2001, Lee *et al*. 2001), multiple sclerosis (Schwid *et al*. 2002), cancer (Dhruva *et al*. 2010, Miaskowski *et al*. 2008) and other chronic diseases (Lerdal 2002).

Despite the evidence for diurnal fluctuations in fatigue, most prior research on HIV-related fatigue has not examined patterns of fatigue, but has instead assessed average fatigue levels across time, such as the past week or month (i.e., Pence *et al*. 2008, Henderson *et al*. 2005) 0. The lack of information about the diurnal pattern of fatigue has implications for assessment, etiology and intervention strategies.

HIV-related fatigue has been associated with socio-demographic and clinical factors, although findings have not been consistent across studies. In some studies, fatigue was associated with gender (Voss 2005), race (Lee *et al*. 2009, Voss 2005) and employment (Barroso *et al*. 2010). Lower CD4+ T-cell count has been associated with higher fatigue, particularly in the evening (Lee *et al*. 1999), but others found no association with CD4+ T-cell count (Barroso *et al*. 2003). Anti-retroviral use and longer time since diagnosis have been associated with lower fatigue (Pence *et al*. 2009).

Several co-morbid symptoms have also been associated with fatigue, including disturbed sleep (Lee *et al*. 2001), depression or anxiety (Barroso *et al*. 2003, Sewell *et al*. 2000, Barroso *et al*. 2010, Jong *et al*. 2010), pain (Aouizerat *et al*. 2009, Creavin *et al*. 2010) and

cognitive complaints (Millikin *et al*. 2003, Woods *et al*. 2007). These symptoms have also been commonly reported by adults living with HIV/AIDS (Lee *et al*. 2009). Although relationships between fatigue and other symptoms have been well-documented, research has not addressed diurnal fatigue patterns. It remains unclear if these co-morbid symptoms are associated with specific fatigue patterns. Different types of fatigue (Dimsdale *et al*. 2003, Dimsdale *et al*. 2007, Nikolaus *et al*. 2010) have been described in an effort to better understand this complex multi-dimensional symptom. However, to assess a patient's fatigue, more knowledge is needed about diurnal patterns and how these patterns relate to other symptoms and clinical factors.

The aims of this study were to:

1. describe patterns of morning and evening fatigue in adults with HIV/AIDS,
2. identify socio-demographic and clinical variables and co-morbid symptoms associated with diurnal patterns of fatigue and
3. determine how diurnal fatigue patterns influence fatigue-related distress and interference in functioning.

Methods

Data were collected as part of a prospective longitudinal study of adults living with HIV in the San Francisco area (Lee *et al*. 2009). The study was designed to characterise the symptom experience of HIV-positive adults and identify associated biological and genetic markers. This analysis reports on morning and evening fatigue ratings collected at the baseline assessment in relation to demographic and clinical characteristics and measures of symptom experience.

Sample and Procedures

A convenience sample of 350 adults with HIV was enrolled in the study over a 3-year period (April 2005 - December 2007). The participants were recruited using flyers posted at local HIV clinics and community sites. Study visits were conducted at the University of California, San Francisco, Clinical Research Center. Eligible participants were English-speaking, at least 18 years old and diagnosed with HIV at least 30 days before enrollment. Individuals were excluded if they currently used illicit drugs, worked nights, had been pregnant in the previous three months, or reported having a diagnosed sleep disorder, bipolar disorder, schizophrenia, or dementia.

Measures

The questionnaires included demographic information on age, gender, race/ethnicity, level of education, partner status and employment status. Participants also reported whether they had ever received a diagnosis of AIDS. With the patient's written authorisation, the most recent CD4+ T-cell counts and viral load levels were obtained from the patient's health care provider. Participants also provided urine samples for toxicology screening using RediCup® (Redwood Toxicology Laboratory, Inc, Santa Rosa CA, USA).

A 4-item version of the Lee Fatigue Scale (LFS) (Lee *et al*. 1991) was used to assess diurnal variations in fatigue. In a previous sample (Lee *et al*. 1991), these 4 items were highly correlated with the 13-item fatigue scale (r=0.95 for morning and 0.91 for evening ratings). Participants completed the LFS within 30 minutes of awakening to measure morning fatigue and within 30 minutes prior to going to sleep to measure evening fatigue for three consecutive days. Morning and evening fatigue scores were calculated as the mean of the four items across the three days and could range from 0-10, with higher scores indicating

greater fatigue. The LFS has been used to measure fatigue in healthy individuals (Gay *et al*. 2004, Lee *et al*. 1991), as well as in patients with cancer (Miaskowski *et al*. 2008) and HIV (Lee *et al*. 1999) and has established validity and internal consistency. In this sample the Cronbach α was 0.93 for the morning and 0.88 for the evening ratings.

The Memorial Symptom Assessment Scale (MSAS) was used to assess symptom experience in the past week (Portenoy *et al*. 1994). It is a reliable and valid self-report measure that has been used in various clinical populations (Blinderman *et al*. 2008, Sawicki *et al*. 2008), including patients with HIV (Harding *et al*. 2006). The MSAS evaluates symptom prevalence, frequency, severity and distress using four or five-point Likert scales. Individual symptom scores were computed for each symptom as the average score on the severity, frequency and distress scales. Fatigue, sleep disturbance, pain, anxiety, depression and cognitive complaints were the most prevalent symptoms in this sample (Lee *et al*. 2009). For this analysis, only the pain symptom score and the distress rating for the 'lack of energy' item were used. If the respondent did not report pain or lack of energy in the past week, the symptom score and distress rating were assigned a value of 0. Symptom scores of 2 or higher indicate moderate to severe pain or fatigue that is somewhat to very distressing.

Fatigue interference during the last week was measured with the FSS-7 (Lerdal *et al*. 2010a) (in review), a Rasch measure based on five items from the Fatigue Severity Scale (Krupp *et al*. 1989). Each item was rated on a numeric rating scale from 1 (strongly disagree) - 7 (strongly agree) and the items were averaged to yield a score from 1 (no fatigue interference) - 7 (extreme fatigue interference). The FSS has well-established test-retest reliability and clearly differentiates between patients with chronic disease and healthy adults (Krupp *et al*. 1989). In this study, Cronbach alpha for the FSS was 0.93. The FSS-7 Rasch measure was used because it was recently found to have better psychometric properties than the original FSS among adults living with (Lerdal *et al*. 2010a) (in review). The five items retained in the Rasch measure all pertain to how fatigue interferes with functioning (e.g., Fatigue interferes with work, family, or social life).

The 19-item Pittsburgh Sleep Quality Index (PSQI) was used to assess perceived sleep disturbance in the past month (Buysse *et al*. 1989). The PSQI has demonstrated test-retest reliability and validity (Backhaus *et al*. 2002, Buysse *et al*. 1989). It yields seven component scores representing different aspects of sleep and subscale scores are summed to yield a total score ranging 0-21. A total score >5 has been designated as a sensitive and specific cutpoint for distinguishing poor sleepers (Buysse *et al*. 1989).

The Center for Epidemiological Studies-Depression Scale (CES-D) (Radloff 1977) was used to assess frequency of depressive symptoms in the past week. The CES-D has acceptable reliability and validity (Radloff 1977) and has been frequently used in the HIV population (Cockram *et al*. 1999, Vosvick *et al*. 2010). Twenty symptoms are rated on frequency in the past week: 0 (rarely or none of the time, <1 day) - 3 (most or all of the time, 5-7 days in the past week). Item scores are then summed to yield a total score ranging from 0-60, with higher scores indicating more depressive symptoms. A cut-off score of 16 is used to indicate a need for further referral to evaluate depression (Cook *et al*. 2002). In this study, the Cronbach alpha coefficient for the CES-D was 0.88.

The Profile of Moods State (POMS) Tension-Anxiety subscale (McNair *et al*. 1971) was used to assess anxiety in the past week. The 9-item subscale scores can range from 0-36, with 8.6 as the mean in HIV-infected outpatients (Illa *et al*. 2008). The POMS has well-established concurrent and construct validity. In this study, the Cronbach alpha coefficient was 0.86.

Participants completed the six-item cognitive function scale from the Medical Outcome Study (MOS) Health-Related Quality of Life (HRQOL) measure (Stewart *et al*. 1992). This self-report instrument has been used in previous studies of HIV-infected adults to measure perceived cognitive function and is valid and reliable (Wu *et al*. 1993, O'Dell *et al*. 1998). Respondents are asked to indicate how often in the past month they experienced difficulties with concentration, attention, forgetfulness and confusion. Each item was rated from 1 (all of the time) to 6 (none of the time). Scores are transformed to a 0-100 scale, with higher scores indicating better cognitive function. The Cronbach alpha coefficient for this sample was 0.91.

Statistical analysis

All analyses were conducted using SPSS version 18.0 (SPSS, Inc, Chicago IL, USA). Square root transformations were used to normalise skewed distributions of scores on the CES-D and POMS subscale and a logarithmic transformation was used to normalise viral load values. Descriptive statistics were used to summarise mean morning and evening fatigue scores across three days. Because there are no validated cutoff scores indicating clinically significant morning or evening fatigue for adults living with HIV, we used a median split to group participants based on their self-report scores: 1) low morning and evening fatigue, 2) high morning fatigue, 3) high evening fatigue, or 4) high morning and evening fatigue. The fatigue groups were compared on demographic and clinical characteristics and symptom experience measures using chi-square or ANOVA with Scheffe post-hoc testing. ANOVA results were confirmed with the Kruskal-Wallis non-parametric test. Demographic variables were analyzed using levels described in Table 1. When applicable, both continuous variables and clinically meaningful categories were evaluated (e.g., CD4+ T-cell count <200 cells/mm^3 and detectable viral load).

Logistic regression analyses were conducted to identify the unique contributions of demographic and clinical characteristics to each fatigue pattern using the low morning and evening fatigue group as the reference. Race, gender, anti-retroviral therapy and CD4+ T-cell count were included in all three models based on associations with fatigue in prior research. In addition, variables in Table 1 associated with fatigue patterns in bivariate analyses ($p< 0.10$) were retained for multivariable analysis. Variables that did not have unique contributions ($p< 0.20$) to any of the three fatigue patterns were dropped from the model. Demographic, clinical and symptom variables were entered in separate steps to evaluate the variance explained by each domain. Potential interactions between race, gender and clinical characteristics were also assessed. For all analyses, $p< 0.05$ was considered statistically significant.

Ethics

The study was approved by the Committee on Human Research at the University of California, San Francisco. All participants provided written informed consent and written authorisation for their health care providers to release their medical records for research purposes.

Results

Sample characteristics

Of the 350 adults with HIV enrolled in the larger study, one was excluded after being unable to submit a urine sample for drug screening and 31 were excluded after screening positive for illicit drugs (cocaine, amphetamine, ecstasy, methamphetamine, or phencyclidine). Demographic and clinical characteristics for the 318 participants included in the final sample are presented in Table 1. The sample was ethnically diverse and predominantly male,

reflecting the local population of adults with HIV. Over half (61%) of the 78 women were African American. Most participants had been living with HIV for many years and were currently on anti-retroviral therapy. They were taking an average of 6.5 (SD4.3) medications (median 6, range 0-25), 51% had been diagnosed with AIDS and 28% with an AIDS diagnosis had a current CD4+ T-cell count of <200 cells/mm^3. Employment rates were low (15%) and most (75%) were receiving medical disability assistance.

Fatigue Ratings

The morning and evening fatigue ratings were stable across the three days, with intraclass correlation coefficients of 0.80 for the three morning ratings and 0.81 for the evening ratings. Mean morning and evening fatigue ratings are presented in Table 2. The morning and evening ratings were correlated ($r=0.64$, $p<0.001$), but as expected, evening ratings were significantly higher than morning ratings (Paired $t[317]=15.3$, $p<0.001$). Those who reported high morning fatigue were also likely to report high evening fatigue (36%), but almost 30% reported only high morning or high evening fatigue. Another 35% reported low levels of both morning and evening fatigue.

The morning and evening fatigue ratings across the three days (six ratings total) are illustrated in Figure 1. Each group has a distinct pattern of fatigue and the pattern was consistent across the three days. The low morning and evening pattern had a rhythm of higher fatigue in the evening, with lower fatigue in the morning and all fatigue ratings are relatively low. The high evening fatigue pattern had the most extreme fluctuation between morning and evening and the high morning fatigue pattern had almost no fluctuation. The high morning and evening fatigue pattern had a strong rhythm, but with consistently high fatigue ratings.

The four fatigue patterns were compared on demographic and clinical characteristics, as well as symptom measures (Table 1). Race was the only demographic characteristic that differed by fatigue pattern, with African-American participants being over-represented in the low fatigue group and under-represented in the high morning and evening fatigue group compared with Caucasians. There was no gender difference in fatigue and fatigue categories did not differ on any of the clinical characteristics evaluated.

The four fatigue patterns differed on all of the co-morbid symptoms assessed (Table 1). In general, those reporting both morning and evening fatigue experienced the worst symptoms, followed closely by those with morning fatigue only. For most symptoms, the experience of those with low fatigue did not differ from those only reporting evening fatigue.

Multivariate Analyses of Fatigue Patterns

Logistic regression analyses are presented in Table 3. Pain and cognitive complaints were not associated with fatigue patterns when controlling for other factors and were excluded from regression models. Interactions of demographic and clinical variables were evaluated for each fatigue pattern and were only in regression models if $p< 0.10$.

Evening fatigue pattern—Anxiety was the only significant predictor of the high evening fatigue pattern (without morning fatigue) when controlling for other factors. Those with high anxiety were 3 times more likely to have the evening fatigue pattern compared with those reporting lower levels of anxiety. Race, anti-retroviral therapy and CD4+ T-cell count made small contributions to the evening fatigue model. African-Americans had slightly lower risk and those taking anti-retroviral therapy had somewhat higher risk of having the evening fatigue pattern. Contrary to expectation, the evening fatigue pattern was slightly more common among those with higher CD4+ T-cell counts (≥200), who were also more likely to

be employed than those with lower counts (18% vs 2% $\chi 2=8.82$, p=0.003). While the model was statistically significant, it only explained 17.5% of the variance in evening-only fatigue.

Morning fatigue pattern—Predictors of high morning fatigue (without evening fatigue) included elevated symptoms of both depression and anxiety. Clinically significant depressive symptoms (CES-D ≥ 16) and higher anxiety (POMS-anxiety ≥ 8.6) were each associated with nearly 3 times the risk of morning-only fatigue. Like the evening fatigue model, African-Americans had a slightly reduced risk and taking ant-retroviral therapy had a slightly increased risk of morning fatigue, but the unique contributions of these variables were not statistically significant. The overall model was significant and explained about 29% of the variance in morning-only fatigue.

High morning and evening fatigue pattern—This pattern was the only one significantly associated with demographic, clinical and symptom factors. African-Americans had a significantly lower risk of this pattern compared with participants of other races. Although this pattern was generally associated with higher CD4+ T-cell count (≥200) and taking anti-retroviral therapy, these effects were considerably confounded by gender. Interaction effects in this model indicate that among women, this fatigue pattern was associated with lower CD4+ T-cell counts and *not* taking anti-retroviral therapy. This pattern was also significantly associated with other symptoms. As in the previous model, anxiety and depression were associated with greater risk. This is the only pattern where sleep disturbance emerged as an independent predictor. Anxiety was associated with nearly three times the risk and depression and sleep disturbance were each associated with more than twice the risk of having high morning and evening fatigue. The regression model was significant and explained 41% of the variance.

Fatigue-related distress and interference with functioning

Table 4 compares levels of fatigue-related distress and interference in functioning across the four fatigue patterns. Compared with the other three groups, the group with both morning and evening fatigue experienced more distress and reported the most interference with functioning. Those with low fatigue, or evening-only fatigue, reported the least distress and interference and these two groups did not differ on interference with functioning.

Discussion

To our knowledge, this is the first study to identify different diurnal patterns of fatigue and explore their relationships with socio-demographic and clinical variables, other symptoms and fatigue-related distress and interference. The patterns of fatigue differed significantly on all of the symptom measures, with the high morning and evening fatigue pattern reporting the highest levels of depression, anxiety, pain, cognitive complaints and sleep disturbance. Because these symptoms are highly correlated with each other, multivariate analyses were conducted to identify the independent contributions of each symptom and each pattern was found to have a unique set of symptom predictors. In addition, each pattern was associated with varying degrees of fatigue-related distress and fatigue-related interference in functioning.

High evening fatigue pattern: Anxiety

Anxiety was the only factor independently associated with the high evening fatigue pattern and those with anxiety were 3 times more likely to have the high evening pattern than the low morning and evening pattern when controlling for other factors. In addition, those with high evening fatigue showed the largest fluctuation between morning and evening compared with other groups (Fig. 1). This large difference may indicate that while much energy is used

during the day, sleep is quite effective at relieving their fatigue. The relatively low symptom burden in the high evening fatigue group suggests that fatigue in the evening is not necessarily problematic as long as sleep is restorative and results in substantially lower morning fatigue ratings. Furthermore, this type of fatigue might be considered a more healthy form of tiredness since it is relieved by sleep (Lee *et al*. 1994).

High morning fatigue pattern: Anxiety and depression

The morning fatigue pattern was not only predicted by anxiety, it was also associated with depressive symptoms, even when controlling for demographic, clinical and other symptoms. Those with clinically significant depressive symptoms (CES-D ≥ 16) were nearly three times more likely to have the morning fatigue pattern, as were those reporting high anxiety. As shown in Fig. 1, this group had a distinct pattern of nearly no fluctuation between morning and evening. This pattern suggests that sleep fails to provide relief from fatigue, but also that little energy is used during the day, since fatigue ratings do not increase later in the day. This pattern was associated with significant symptom burden and the group did not differ from the more debilitating high morning and evening fatigue pattern on any symptom measure. Diagnostic criteria for depression include early morning worsening of symptoms among its melancholic features(American Psychiatric Association 2000), which is consistent with the relatively high level of morning fatigue in this group. A pan-European survey of depression in the community (Tylee *et al*. 1999) showed that tiredness was recorded by 73.5% of those with depression and that tiredness was the second most prevalent symptom among depressed adults.

High morning and evening fatigue pattern: Anxiety, depression and sleep disturbance

The high morning and evening fatigue pattern was the most debilitating, distressing and clinically complex type of fatigue identified in this study. In addition to anxiety and depression, sleep disturbance was also a significant predictor of this pattern. This group was nearly three times more likely to have anxiety, more than twice as likely to have clinically significant depressive symptoms and more than twice as likely to have disturbed sleep compared with those in the low morning and evening fatigue group when controlling for other factors. Demographic and clinical factors were also significant predictors of this pattern and clinical predictors differed by gender, highlighting the importance of examining interactions to fully understand these complex relationships. Even though the high morning and evening pattern had relatively normal daily fluctuations, fatigue ratings were consistently higher than average. The significance of sleep disturbance in this model suggests that this pattern may be a type of sleep-related fatigue where sleep disturbance plays a key role in the etiology.

Anxiety and fatigue

Anxiety was a consistent predictor of fatigue regardless of fatigue's diurnal pattern. This finding supports previous studies reporting a relationship between fatigue and anxiety, psychological distress and stress (Paddison *et al*. 2009, Salahuddin *et al*. 2009, Phillips *et al*. 2004, Leserman *et al*. 2008). In one recent study (Theuninck *et al*. 2010) HIV diagnosis, treatment and physical symptoms were strongly associated with post-traumatic stress disorder (PTSD), which has an estimated prevalence of 30–60% among adults with HIV (Theuninck *et al*. 2010, Reisner *et al*. 2009, Whetten *et al*. 2008). Studies have also reported an association between PTSD symptoms and fatigue in HIV-infected adults (Barroso *et al*. 2010) and in the general population (Lerdal *et al*. 2010b). Our findings indicate that psychological distress (anxiety, stress, or PTSD symptoms) is an important antecedent to fatigue in HIV-infected adults.

Depression and Fatigue

The relationship between depression and fatigue is well-documented (Barroso *et al*. 2010, Corless *et al*. 2008, Jong *et al*. 2010, Phillips *et al*. 2004, Voss *et al*. 2007, Millikin *et al*. 2003, Walker *et al*. 1997). However, this study clarified that the relationship may be specific to morning fatigue, regardless of evening fatigue levels. In this sample, those reporting evening-only fatigue did not differ from those in the low morning and evening fatigue group on the CES-D. Although depression and fatigue have conceptual overlap (Voss *et al*. 2007), our study showed that different fluctuating patterns distinguish between the two concepts.

Sleep Disturbance and fatigue

Previous studies have documented a relationship between sleep disturbance and fatigue (Salahuddin *et al*. 2009, Lee *et al*. 2001, Lee *et al*. 1999, Phillips *et al*. 2004, Pence *et al*. 2008). In this study, sleep disturbance was associated with all three patterns in bivariate analyses. However, in multivariate analyses controlling for demographic, clinical and other symptom factors, sleep disturbance was only a significant independent predictor of the high morning and evening fatigue pattern. This finding is consistent with previous research showing that poor sleep is associated not only with greater fatigue the next morning, but also with more fatigue the following evening (Lee *et al*. 1999). A study of healthy adults (Morris *et al*. 1992) showed a higher level of fatigue in the morning among people who were sleep deprived, while those without sleep deprivation had slightly lower fatigue ratings in the morning than in the evening, indicating that sleep disturbance can influence patterns of fatigue. The finding that sleep disturbance was not independently associated with either evening-only or morning-only fatigue suggests that bivariate relationships between sleep disturbance and these two fatigue patterns may be better explained by psychological symptoms rather than sleep disturbance specifically.

Pain, cognitive complaints and fatigue

Although pain and cognitive complaints differed across fatigue groups in bivariate analyses, neither symptom was uniquely predictive of any fatigue pattern when controlling for other factors. We previously reported that those with pain in this sample had higher levels of fatigue interference than those without pain (Aouizerat *et al*. 2010). However, in this analysis, pain was only related to fatigue patterns in bivariate analyses and did not contribute to multivariate models. The finding that pain is not a unique predictor of fatigue pattern is consistent with another study in HIV-infected adults (Paddison *et al*. 2009). Cognitive complaints have also been associated with fatigue (Woods *et al*. 2007), and while they differed across fatigue patterns in bivariate analyses in this study, their nonsignificance in multivariate models highlights the importance of controlling for other factors when identifying correlates of fatigue.

Demographics and fatigue

In this study, African Americans reported lower morning and evening fatigue than Caucasians and other races. Therefore, African Americans were over-represented in the low morning and evening fatigue group and under-represented in the high morning and evening group. This finding is consistent with other studies reporting lower symptom burden (Phillips *et al*. 2004, Silverberg *et al*. 2009) and lower fatigue (Voss 2005, Henderson *et al*. 2005) among African-Americans with HIV. Additional research is needed to better understand whether this phenomenon is due to under-reporting of symptoms or to better coping and social support among African-Americans compared with others.

Gender was unrelated to fatigue patterns in bivariate analyses, but was an important moderator of clinical factors in the multivariate model of morning and evening fatigue

pattern. Although some have found more fatigue among HIV-infected women than men (Voss 2005), most have not identified gender differences in HIV-related fatigue (Henderson *et al*. 2005). Gender difference in fatigue in the general population has a very small effect size (Lerdal *et al*. 2010b), indicating a weak relationship. It is likely that the stress of living with HIV would mask any subtle gender difference in fatigue.

Our findings were also consistent with a previous study indicating no relationship between fatigue and age (Voss *et al*. 2007). Previous studies (Voss 2005, Lee *et al*. 1999) documented an association between fatigue and employment, but this was not observed in our sample. There were also no differences between those with and without children in this study, in contrast to previous findings (Lee *et al*. 1999).

Clinical factors and fatigue

Clinical variables had complex relationships with the different fatigue patterns and the relationships were evident in multivariate analyses after controlling for demographic variables. Anti-retroviral therapy was associated with *higher* risk of the three different fatigue patterns, although among women, it was associated with a *lower* risk of the morning and evening fatigue pattern. Similarly, low CD4+ T-cell count was associated with lower risk for two of the three fatigue patterns, except that among women it was associated with substantially *higher* risk for the high morning and evening pattern. Our findings are not surprising given the inconsistent results of prior studies (Henderson *et al*. 2005, Darko *et al*. 1992, Lee *et al*. 1999, Phillips *et al*. 2004, Barroso *et al*. 2010). Consistent with other studies, viral load (Henderson *et al*. 2005, Barroso *et al*. 2010) was unrelated to fatigue pattern in this sample.

Study limitations

As a cross-sectional and correlational study, causal interpretations need to be made with caution. Longitudinal studies will facilitate greater understanding of how fatigue and other symptoms develop and influence one another over time. In future studies, it would be warranted to include larger samples who report morning-only or evening-only fatigue to have more statistical power for multivariate analyses. This study was limited to fatigue values over three days, thereby restricting the variability of patterns observed. Studies of fatigue throughout the 24-hour cycle and over longer periods of time could determine whether additional patterns exist (Dimsdale *et al*. 2003).

Implication for research and theory development

Our review of research on HIV-related fatigue showed that diurnal patterns have not been adequately or empirically studied, despite the availability and use of morning and evening fatigue measures and despite fluctuation being described as one characteristic of fatigue in inductive theory development (Lerdal 2002). Further examination is warranted to explore different patterns of fatigue fluctuation in relation to level of physical activity, sleep-wake patterns and circadian rhythms. Since the most clinically problematic fatigue pattern was associated with several symptoms previously identified as part of a recognised symptom cluster, studies should investigate possible symptom clusters and explanatory models for these various fatigue patterns (Dodd *et al*. 2004). Future research should also evaluate whether available treatments are more effective for some fatigue patterns than others. Randomised clinical trials that test a tailored approach toward reducing fatigue based on its pattern of expressive would be more likely to yield better results than a more generic intervention approach.

Conclusion

This study has shown that clinicians and researchers need to consider patterns of fatigue to distinguish normal fluctuations in energy level from clinically significant fatigue related to other severe symptoms (such as anxiety, depression and sleep disturbance), distress and interference with activity in daily life. Testing or implementing intervention strategies would have better outcomes in reducing fatigue if they are tailored toward the pattern of fatigue experienced by the patient.

Relevance to clinical practice

Fatigue can be a healthy symptom for adults who feel tired at the end of the day. In this case, fatigue serves as a healthy reminder to rest. When fatigue is relieved by sleep or rest, fatigue would be considered a healthy symptom experience. Our findings in a clinical sample of adults with HIV/AIDS demonstrate that fatigue is less likely to be related to their clinical disease and more likely to be related to mental health symptoms of depression and anxiety. Our data indicate that anxiety can be fatiguing and nurses should assess for anxiety when patients who have any type of chronic illness complain of fatigue. These results provide initial evidence for the importance of assessing the patient's daily fluctuation in fatigue, as different patterns can be associated with different symptom experiences and perhaps different etiologies.

The most severe and debilitating types of fatigue (those with severe morning and evening fatigue and those with morning-only fatigue) should be further evaluated for potential sleep problems that may include non-restorative sleep. A more detailed assessment of the patient's rest-activity patterns associated with their fatigue pattern can provide important clinical information when planning and prescribing appropriate levels of rest and activity as well as self-care behaviors to cope with excessive fatigue. Nurses should also consider the need for referral to a sleep disorders expert if fatigue is not relieved by a night of sleep (Lee & Ward 2005). Different fatigue patterns may benefit more from tailored intervention strategies to reduce symptoms of anxiety or depression than from prescriptions to 'get plenty of rest.' Management strategies for coping with anxiety or depressive symptoms, or strategies for addressing inadequate or disturbed sleep patterns should be targeted for patients who experience high levels of morning fatigue.

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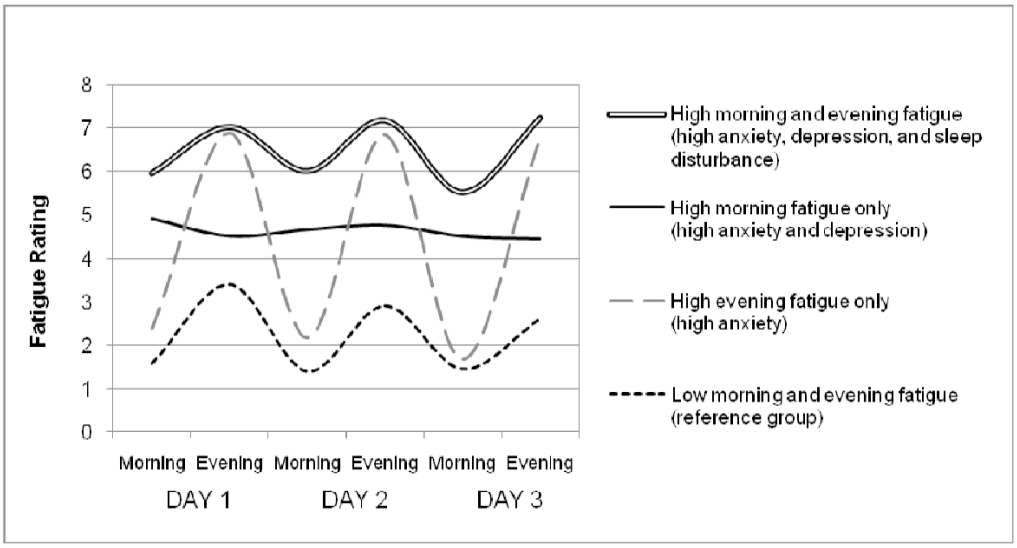

Figure 1.
Mean morning and evening fatigue ratings over 3 days for the four fatigue patterns. The symptoms uniquely associated with each pattern are included in the legend.

Table 1

Sample demographics, clinical characteristics, and symptom experience by fatigue pattern

		Fatigue Pattern				
	Full Sample (N=318)	**A Low morning and evening (n=111)**	**B High evening only (n=46)**	**C High morning only (n=47)**	**D High morning and evening (n=114)**	**Test statistic p-value**
DEMOGRAPHIC						
Age	45.1 (8.3)	45.6 (8.3)	45.4 (7.1)	43.6 (9.5)	45.2 (8.3)	$F = 0.62$; $p = .601$
Gender						$\chi^2 = 6.84$; $p = .336$
Male	68%	61%	72%	66%	74%	
Female	25%	28%	26%	26%	21%	
Transgender	7%	11%	2%	8%	5%	
Race						$\chi^2 = 34.7$; $p < .001$
African-American	39%	59%^{D}	33%	36%	23%^{A}	
Caucasian	41%	27%^{D}	46%	34%	54%^{A}	
Other	21%	14%	22%	30%	23%	
Employed/in school	15%	14%	13%	17%	18%	$\chi^2 = 1.00$; $p = .802$
Has children	36%	43%	33%	38%	29%	$\chi^2 = 5.33$; $p = .149$
CLINICAL VARIABLES						
CD4+ T-cells/mm^3 (n=303)						
Mean count of cells/mm^3	449 (265)	416 (257)	483 (274)	480 (260)	455 (272)	$F = 0.62$; $p = .304$
% < 200 cells/mm^3	17%	19%	9%	24%	18%	$\chi^2 = 3.55$; $p = .314$
Viral load, copies/mL (n=296)						$\chi^2 = 5.07$; $p = .535$
undetectable	50%	46%	52%	49%	55%	
detectable – 9,999	30%	31%	36%	34%	25%	
≥ 10,000 copies/mL	20%	23%	11%	17%	20%	
Years since HIV diagnosis	12.0 (6.7)	11.7 (6.3)	12.3 (6.8)	10.1 (7.6)	13.0 (7.2)	$F = 2.09$; $p = .102$
AIDS diagnosis	52%	44%	59%	51%	58%	$\chi^2 = 5.17$; $p = .160$
Taking anti-retroviral therapy	70%	63%	74%	72%	75%	$\chi^2 = 4.62$; $p = .202$
Body Mass Index	27.0 (5.5)	26.9 (5.2)	27.1 (7.5)	28.6 (5.2)	26.4 (5.0)	$F = 1.87$; $p = .134$
RELATED SYMPTOMS						
Depression (CES-D)						

		Fatigue Pattern				
	Full Sample (N=318)	**A Low morning and evening (n=111)**	**B High evening only (n=46)**	**C High morning only (n=47)**	**D High morning and evening (n=114)**	**Test statistic p-value**
Mean score (SD)	16.9 (10.4)	12.4 (9.4)^{C,D}	15.5 (10.8)^{D}	20.0 (8.6)^{A}	20.5 (10.3)^{A,B}	$F = 17.7$; $p < .001$
% ≥ 16	50%	32%	40%	72%	61%	$\chi^2 = 30.1$; $p < .001$
Anxiety (POMS)						
Mean score (SD)	8.7 (7.0)	5.3 (5.7)^{B,C,D}	9.2 (7.7)^{A}	10.6 (5.9)^{A}	11.0 (7.2)^{A}	$F = 20.7$; $p < .001$
% > HIV norm of 8.6	42%	20%	44%	58%	56%	$\chi^2 = 35.3$; $p < .001$
Cognitive Function (MOS)						
Mean score (SD)	70 (24)	77 (22)^{D}	70 (25)	67 (23)	63 (24)^{A}	$F = 0.62$; $p < .001$
% < median of 77	48%	34%	47%	55%	58%	$\chi^2 = 13.9$; $p < .003$
Pain score (MSAS)						
Mean score (SD)	1.4 (1.4)	1.2 (1.3)^{D}	1.1 (1.3)^{D}	1.4 (1.3)	1.7 (1.5)^{A,B}	$F = 4.59$; $p = .004$
% ≥ 2 (moderate pain)	41%	33%	31%	41%	53%	$\chi^2 = 11.1$; $p = .011$
Sleep disturbance (PSQI)						
Mean score (SD)	7.6 (3.8)	6.3 (3.4)^{C,D}	6.5 (3.3)^{C,D}	8.7 (4.0)^{A,B}	8.9 (3.6)^{A,B}	$F = 13.5$; $p < .001$
% > 5	66%	54%	56%	77%	78%	$\chi^2 = 19.1$; $p < .001$

Note: CES-D=Center for Epidemiologic Studies-Depression Scale; POMS=Profile of Mood States – Tension-Anxiety Subscale; MOS=cognitive subscale from the Medical Outcomes Study; MSAS=Memorial Symptom Assessment Scale; PSQI=Pittsburgh Sleep Quality Index

Exponents indicate groups that differed significantly in post-hoc testing:

^{A}differed from Low morning and evening group

^{B}differed from High evening-only group

^{C}differed from High morning-only group

^{D}differed from High morning and evening group

Table 2

Morning and evening fatigue ratings by fatigue category

		Fatigue Category				
	Full Sample (N=318)	**A Low morning and evening (n=111)**	**B High evening only (n=46)**	**C High morning only (n=47)**	**D High morning and evening (n=114)**	**Test statistic p-value**
FATIGUE RATINGS	N=318	N=111	N=46	N=47	N=114	
Morning mean (SD)	3.6 (2.3)	1.5 (1.0)^{C,D}	2.1 (1.0)^{C,D}	4.7 (0.8)^{A,B,D}	5.8 (1.5)^{A,B,C}	$F = 278.2$; $p < .001$
Evening mean (SD)	5.3 (2.2)	3.0 (1.5)^{B,C,D}	6.8 (0.8)^{A,C}	4.6 (0.8)^{A,B,D}	7.1 (1.1)^{A,C}	$F = 275.6$; $p < .001$

Note: Exponents indicate groups that differed significantly in post-hoc testing, as in Table 1.

Table 3

Multiple logistic regression analysis of fatigue patterns

	Model					
	High Evening Only		High Morning Only		High Morning and Evening	
PREDICTORS	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Step 1 – Demographics	ΔR^2 = .048	.086	ΔR^2 = .051	.073	ΔR^2 = .169	<.001
Race (African-American)	0.49 (0.21, 1.13)	.094	0.38 (0.15, 1.01)	.053	0.22 (0.11, 0.46)	<.001
Gender (Female)	0.89 (0.32, 2.45)	.817	1.60 (0.57, 4.47)	.371	1.61 (0.44, 5.82)	.471
Step 2 – Clinical	ΔR^2 = .068	.025	ΔR^2 = .042	.109	ΔR^2 = .023	.114
CD4+ count <200 cells/mm^3	0.23 (0.05, 1.12)	.069	1.87 (0.68, 5.12)	.224	0.32 (0.11, 0.91)	.032
Anti-retroviral therapy	2.36 (0.97, 5.74)	.058	2.45 (0.94, 6.35)	.066	3.31 (1.39, 7.88)	.007
Step 3 – Interactions*	-	-	-	-	ΔR^2 = .047	.012
Gender by CD4+	-	-	-	-	43.1 (3.9, 472.5)	.002
Gender by therapy	-	-	-	-	0.18 (0.03, 1.00)	.050
Step 4 – Other Symptoms	ΔR^2 = .059	.085	ΔR^2 = .195	<.001	ΔR^2 = .173	<.001
Anxiety (POMS ≥ 8.6)	3.05 (1.13, 8.20)	.027	2.91 (1.13, 7.52)	.028	2.91 (1.34, 6.32)	.007
Depression (CES-D≥ 16)	0.97 (0.35, 2.68)	.960	2.79 (1.06, 7.38)	.038	2.37 (1.09, 5.15)	.030
Sleep disturbance (PSQI>5)	0.96 (0.42, 2.18)	.918	1.66 (0.65, 4.24)	.288	2.28 (1.11, 4.68)	.025
OVERALL MODEL FIT	χ^2=18.89	.009	χ^2=32.19	<.001	χ^2=79.21	<.001
Pseudo R^2	.175		.288		.412	

Note. Low morning and evening fatigue group is the reference group; OR=Odds ratio; POMS=Profile of Mood States – Tension-Anxiety Subscale; CES-D=Center for Epidemiologic Studies-Depression Scale; PSQI=Pittsburgh Sleep Quality Index);

*Interactions between demographic and clinical variables were only included in the model if p<.10

Table 4

Fatigue-related distress and interference by fatigue category

		Fatigue Category				
	Full Sample	**A Low morning and evening**	**B High evening only**	**C High morning only**	**D High morning and evening**	**Statistic *p*-value**
FATIGUE EXPERIENCE	N=318	N=111	N=46	N=47	N=114	
Distress (MSAS)	1.55 (1.37)	0.86 (1.13)^{C,D}	1.28 (1.45)^{D}	1.65 (1.27)^{A,D}	2.29 (1.21)^{A,B,C}	$F = 26.0$; $p < .001$
Interference (FSS-7)	3.76 (1.71)	2.89 (1.53)^{C,D}	3.45 (1.71)^{D}	3.91 (1.55)^{A}	4.66 (1.49)^{A,B}	$F = 25.3$; $p < .001$

Note: Exponents indicate groups that differed significantly in post-hoc testing; FSS-7=Fatigue Severity Scale – 7 item version; MSAS=Memorial Symptom Assessment Scale