Fatigue in HIV and AIDS: An Analysis of Evidence

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HIV-related fatigue continues to be the most common complaint of infected people. No physiological factors have been consistent predictors for fatigue; psychosocial factors, particularly depression, have emerged more consistently in studies. While clinicians would want to rule out common causes of fatigue such as hypothyroidism, hypogonadism, or anemia, there is scant research for most interventions, which makes it difficult to make definitive recommendations for their use. Modafinil has the strongest research evidence to date, with multiple studies finding it effective in relieving fatigue. However, researchers must continue to pursue ways to ameliorate fatigue in HIV infection, given the high financial, personal, and social costs suffered by people experiencing it.

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Thirty years into the AIDS epidemic, fatigue remains the most frequent and debilitating complaint of HIV-infected people. There are many definitions of fatigue. The *American Heritage Stedman's Medical Dictionary* (Fatigue, n.d., final paragraph) defined fatigue as "physical or mental weariness resulting from exertion; a sensation of boredom and lassitude due to absence of stimulation, to monotony, or to lack of interest in one's surroundings; or the decreased capacity or complete inability of an organism, an organ, or a part to function normally because of excessive stimulation or prolonged exertion." Nurse scientists have also provided definitions of fatigue. Ream and Richardson (1996), in a classic concept analysis paper, defined fatigue as a subjective, unpleasant symptom that incorporates total feelings ranging from tiredness to exhaustion, creating an unrelenting overall condition that interferes with individuals' abilities to function to their normal capacities. Aaronson and colleagues (1999) defined fatigue as an awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity.

The Epidemiology of HIV-Related Fatigue

There are no data sources that would allow us to determine the incidence of fatigue in HIV infection. We have prevalence data only. Justice, Rabeneck, Hays, Wu, and Bozzette (1999) found fatigue to be the most common symptom among people with HIV infection; it was associated with functional limitation, and the greater the fatigue, the poorer the chances of survival. A study by Sullivan and Dworkin (2003), involving 13,768 people with HIV infection in 10 U.S. cities, found that the prevalence of fatigue was 37%. Fatigue was more common among persons with clinical AIDS, depression, and low hemoglobin. Fatigue was not associated with viral load or a CD4+ T cell count less than 200 cells/mm^3. The authors concluded that fatigue was very common in people with HIV infection and could

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not be viewed solely as a constitutional symptom of progressive HIV disease. Consistent with this view, Holzemer (2002) found that while some HIV-infected people did not develop fatigue until the illness had progressed, others developed it in the early stages of the infection. Paddison, Fricchione, Ghandi, and Freudenreich (2009) found that 80% of HIV-infected patients referred for psychiatric care reported at least moderate fatigue. Jong and colleagues (2010) analyzed 42 studies published since 1996 on predictors or therapy of HIV-related fatigue; they found that the reported HIV-related fatigue prevalence varied from 33% to 88%. In a study of participants who were on antiretroviral therapy, Dacosta Dibonaventura, Gupta, Cho, and Mrus (2012) found that fatigue was the most frequently reported side effect, affecting nearly 71% of a sample of 953 individuals. It is important to remember, however, that this does not necessarily mean that the medications caused the fatigue; the data on the relationship between antiretroviral (ARV) medications and fatigue has been conflicting, with some researchers finding a positive correlation (taking ARV medications was correlated with higher fatigue, e.g., Currier et al., 2008) and others finding a negative correlation (not being on ARV medication was correlated with higher fatigue, e.g., Barroso et al., 2010).

Physiological and Psychosocial Correlates of Fatigue

There is conflicting evidence about possible physiological and psychosocial correlates of fatigue. A lower CD4+ T cell count has been related to greater fatigue in some studies (Darko, McCutchan, Kripke, Gillin, & Golshan, 1992; Lee, Portillo, & Miramontes, 1999; Walker, McGown, Jantos, & Anson, 1997), but not in others (Barroso, Carlson, & Meynell, 2003; Barroso et al., 2010; Breitbart, McDonald, Rosenfeld, Monkman, & Passik, 1998; Henderson, Safa, Easterbrook, & Hotopf, 2005; Justice et al., 1999; Perkins et al., 1995; Sullivan & Dworkin, 2003; Vlahov et al., 1994; Vogl et al., 1999; Voss, 2005). Henderson and colleagues (2005) actually found greater fatigue in individuals with higher CD4+ T cell counts. Some studies found no relationship between fatigue and HIV viral load (Barroso et al., 2003; Barroso et al., 2010; Ferrando et al., 1998; Schifitto et al., 2011; Sullivan & Dworkin, 2003; Voss, 2005), whereas others found greater fatigue with a higher viral load (Safren et al., 2012; Simmonds, Novy, & Sandoval, 2005) or disease progression (Cook, Sousa, Matthews, Meek, & Kwong, 2011). Other researchers have examined the relationship of fatigue to other symptoms; Wantland and colleagues (2011) found that muscle aches, numbness, and fatigue were related in a time-ordered fashion, with muscle aches and numbness preceding fatigue. Aouizerat and colleagues (2010) reported a bivariate correlation between pain and fatigue; however, these findings did not hold up when a regression analysis was conducted.

The search for biomarkers of HIV-related fatigue has been a difficult one. Barroso and colleagues (2010) found no physiological predictors of fatigue in a comprehensive examination of 128 HIV-infected participants over a 3-year period. In more promising work, Voss and colleagues (2011) compared gene expression profiles of $CD14^+$ cells of nucleoside reverse transcriptase inhibitor-treated HIV-infected patients with low versus high fatigue to healthy controls ($n = 5$ each). They identified 32 genes predictive of low versus high fatigue. Schifitto and colleagues (2011), in an examination of 128 HIV-infected patients, found that magnetic resonance spectroscopy revealed significantly lower levels of the cellular energy marker total creatine in the basal ganglia of fatigued participants. Lower cellular energy levels in the basal ganglia, as measured by magnetic resonance spectroscopy total creatine concentration, suggested energy dysmetabolism in this brain region. The authors posited that neuronal circuitry that involved striatal–cortical pathways may play an important role in HIV-associated fatigue and may be amenable to therapeutic intervention (Schifitto et al., 2011).

Psychosocial variables, particularly depression, have consistently been correlated with fatigue. The most common and persistent finding is the strong correlation of depressed mood with fatigue (Barroso, 2001; Barroso et al., 2003; Barroso et al., 2010; Barroso & Lynn, 2002; Breitbart et al.1998; Henderson et al., 2005; Millikin, Rourke, Halman, & Power, 2003; Phillips et al., 2004; Schifitto et al., 2011; Voss, 2005). Indeed, fatigue is part of the symptom complex of major depression and mood disturbance. Fatigue has also been associated with state and trait anxiety (Barroso et al., 2003); some classification systems include fatigue among the criteria for a diagnosis of anxiety (American Psychiatric Association, 2000). In one study, HIV-infected gay men reported more anxiety and stress than the general population, and anxiety and fatigue were related (Sewell et al., 2000). Paddison and colleagues (2009) found that increases in anxiety, stress, and depression were related to increases in HIV-related fatigue in a sample of 38 individuals referred for psychiatric care.

Other psychosocial factors may also contribute to fatigue in infected individuals; for example, HIV-infected gay men who were less satisfied with their social support networks were more likely to be fatigued (Barroso et al., 2002). Stressful life events may also contribute to chronic fatigue (Leserman, Barroso, Pence, Salahuddin, & Harmon, 2008); such events have been associated with anxiety and depression in other populations (Honn & Bornstein, 2002; Murphy, Moscicki, Vermund, & Muenz, 2000; Roberts, Ciesla, Direnfeld, & Hewitt, 2001). Finally, a history of trauma is common among people with HIV infection, and with it comes a number of adverse psychological sequelae, including depression, anxiety, and post-traumatic stress disorder (Whetten, Reif, Whetten, & Murphy-McMillan, 2008), all of which may lead to increases in fatigue.

Poor sleep quality, which likely lives on the margins of psychosocial and physiological factors associated with HIV-related fatigue, has also been a consistent correlate of fatigue. This literature has been most helpful in helping patients see patterns in their fatigue, allowing them to plan their daily activities in a more energy-conserving manner. Different patterns of fatigue may require the tailoring of interventions as well. Lerdal, Gay, Aouizerat, Portillo, and Lee (2011) found that a high evening fatigue pattern was associated with anxiety, and a high morning pattern was associated with anxiety and depression, and that, while the morning fatigue pattern showed very little fluctuation between morning and evening, the evening pattern showed the largest fluctuation. The high fatigue in both 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 (Lerdal et al., 2011). Similarly, Lee and colleagues (2012) reported that HIV-infected individuals who reported greater sleep disturbance had more morning fatigue. Greater insomnia severity has been associated with greater fatigue, and depression may contribute to both insomnia and fatigue (Low, Preud'homme, Goforth, Omonuwa, & Krystal, 2011). These researchers advocated for the treatment of insomnia in the absence of depression to ameliorate fatigue.

Assessment and Clinical Measurement Tools

Many instruments have been developed to measure fatigue. Aaronson and colleagues (1999) highlighted the difficulty in measuring a construct as subjective as fatigue and noted that different measures tap into different aspects of fatigue. Some instruments simply measure the presence or absence of fatigue; others measure only one aspect of fatigue (e.g., physical fatigue or decreased muscle strength). Some researchers have borrowed tools developed to measure concepts other than fatigue (e.g., performance or vitality). Many of the instruments used to measure fatigue are very brief (four questions or fewer) and, although most of them have acceptable psychometric properties, they do not capture the full experience of HIV-related fatigue as encountered in real-life experience. Therefore, the first author developed the 56-item HIV-Related Fatigue Scale (HRFS), which remains the only instrument developed specifically to measure fatigue in people with HIV infection (Barroso & Lynn, 2002). It was developed through formative qualitative research and designed to measure the intensity and consequences of fatigue as well as the circumstances surrounding fatigue in people living with HIV. Initial psychometric testing of the HRFS in 54 people living with HIV has been reported in an article that included a list of all available fatigue scales that could be located to that point (Barroso & Lynn, 2002). Most of the scales used to measure fatigue today were derived from one of the scales in Table 1 of the article by Barroso and Lynn (2002).

The HRFS has three main scales, which measure fatigue intensity, the responsiveness of fatigue to circumstances, and fatigue-related impairment of functioning (Barroso & Lynn, 2002; Pence, Barroso, Leserman, Harmon, & Salahuddin, 2008). It is important to know both how severe the fatigue is and the degree to which it is interfering with the patient's life. The functioning scale can be further divided into subscales measuring impairment of activities of daily living, impairment of mental functioning, and impairment of social functioning. In a longitudinal study examining the natural course of fatigue in HIV infection (n = 128), each scale demonstrated high internal consistency (Cronbach α = 0.93, 0.91, and 0.97 for the intensity, responsiveness, and functioning scales, respectively). The HRFS scales also demonstrated satisfactory convergent validity when compared to other fatigue measures. Fatigue scales were moderately correlated with quality of nighttime sleep (ρ = 0.46, 0.47, and 0.35) but showed only weak correlations with daytime sleepiness (ρ = 0.20, 0.33, and 0.18). The scales were also moderately correlated with general mental and physical health as measured by the SF-36 Health Survey (ρ ranged from 0.30 to 0.68 across the 8 SF-36 subscales, with most >0.40; Pence et al., 2008). Although the scale is long at 56 items, it can be completed in less than 10 minutes, and scored in less than 5 minutes. Clinicians and researchers who wish to determine fatigue intensity only can use the first seven items. We successfully used the HRFS in our 3-year study of the course of HIV-related fatigue (Barroso et al., 2010).

As mentioned above, other researchers have adapted instruments to measure fatigue. The Global Fatigue Index, used in a study by Bormann, Shively, Smith, and Gifford (2001), was derived from the Multidimensional Assessment of Fatigue, which was originally developed to measure fatigue in patients with rheumatoid arthritis. The Piper Fatigue Scale, also frequently used in studies of HIV-related fatigue (e.g., Low et al., 2011), was developed to measure fatigue in cancer patients. The Fatigue Severity Scale, used by Rabkin, McElhiney, and Rabkin (2011b) and Schifitto and colleagues (2011), was developed for patients with multiple sclerosis and systemic lupus erythematosus. The Lee Fatigue Scale (Lerdal at al., 2011) was used in a study of sleep quality and insomnia, and was derived from the Visual Analogue Scale for Fatigue for patients with sleep disorders. Some authors reported using a quality-of-life scale or a general symptom scale (e.g., Wantland et al., 2011) to measure fatigue.

What Interventions Are Effective for Preventing and Treating Fatigue in People With HIV?

With regard to interventions for HIV-related fatigue, clinicians should first look for possible physiologic causes of fatigue, such as anemia, hypogonadism, or hypothyroidism. If present, these conditions should be treated. Overwhelming evidence points to HIV-related fatigue being unrelated to the CD4+ T cell count or HIV viral load; thus, it appears to be unrelated to stage of infection, and normal values of these markers should not be used to diminish the patient's concerns about fatigue.

Payne, Whiffen, and Martin (2012) conducted a Cochrane Review of fatigue and weight loss in adults with advanced progressive illness, which they defined as conditions for which there was no cure and which had significant morbidity in the latter stages of illness. There is some concern, therefore, that the data they report are not applicable to the majority of people who are HIV-infected and are doing well, who are living with HIV as a chronic manageable illness. In this review, the authors were searching for primary intervention strategies for fatigue, which may have included those that help preserve muscle mass and maintain energy reserves through interventions such as exercise, activity pacing, relaxation, and support services. It is important to note that these criteria would likely not include psychosocial interventions, as they are physiologically focused. The authors included two systematic reviews that included 21 studies and 748 subjects; the interventions were progressive resistive exercise and aerobic exercise. There was a single study, with 60 participants, that found significant decreases in fatigue in exercisers compared to nonexercisers, as measured by an increase in the time on a treadmill, but the participants in the study were not in the advanced stages of illness. Payne and colleagues (2012) noted that there was a lack of robust interventions to treat fatigue.

Fatigue in HIV infection does appear to be different from fatigue suffered by patients with other illnesses. Payne and colleagues (2012), in their Cochrane Review that examined fatigue interventions in multiple illnesses, found that exercise interventions could lead to an improvement in fatigue in people with cancer, and that self-management education programs and respiratory rehabilitation interventions could improve fatigue scores in people with chronic obstructive pulmonary disease. The pharmacological agent amantadine may provide a small improvement in fatigue for some people with multiple sclerosis. With each of these conclusions, the authors stated that the beneficial effects of any of these interventions in advanced illness had yet to be proven. And while the authors called for a uniform measure of fatigue across illnesses to facilitate study comparison, this would lead to a loss of critical data that may help researchers better understand the nuances of fatigue in different diseases. Indeed, it may be these nuances that would help us better target interventions.

Since the earliest days of the epidemic, clinicians and researchers have searched for interventions that might ameliorate fatigue. Thyroid hormone (Derry, 1996), intermittent hyperbaric oxygen therapy (Jordan, 1998; Reillo, 1993), DHEA treatment (Rabkin, Ferrando, Wagner, & Rabkin, 2000), testosterone therapy (Rabkin, Wagner, & Rabkin, 2000; Wagner, Rabkin, & Rabkin, 1998), and psychostimulants such as dextroamphetamine (Wagner & Rabkin, 2000), modafinil (McElhiney, Rabkin, Van Gorp, & Rabkin, 2010; Rabkin, McElhiney, & Rabkin, 2011a; Rabkin, McElhiney, Rabkin, & Ferrando, 2004; Rabkin, McElhiney, Rabkin, & McGrath, 2010), and methylphenidate hydrochloride and pemoline (Breitbart, Rosenfeld, Kaim, & Funesti-Esch, 2001), have all been found somewhat effective in ameliorating fatigue. Relaxation training (Fukunishi et al., 1997) and aerobic exercise (Smith et al., 2001) have also been effective. Self-care measures used to treat HIV-related fatigue have included supplements, vitamins, and nutrition; sleep and/or rest; adjustment to activities, approaches, or thoughts; and exercise (Corless et al., 2002; Siegel, Brown-Bradley, & Lekas, 2004). In a review of treatment strategies, which included most of the studies listed above, Jong and colleagues (2010) noted that studies on treatment strategies were minor in nature and focused on a select group of patients, most of whom had a major depressive disorder or clinical hypogonadism. Modafinil seems to be the treatment with the most evidence to support its use; there have been multiple studies with robust sample sizes conducted by Rabkin and colleagues (e.g., McElhiney et al., 2010; Rabkin et al., 2004; Rabkin et al., 2010; Rabkin, McElhiney, & Rabkin, 2011a; Rabkin, McElhiney, & Rabkin, 2011b), and the results have consistently been reported as being effective in treating HIV-related fatigue.

In the review by Jong and colleagues (2010), the strongest and most uniform associations were observed between fatigue and psychological factors such as depression and anxiety. Many studies point to the persistent coexistence of fatigue and depression (e.g., Kudel, Cotton, Szaflarski, Holmes, & Tsevat, 2011), which also helps to explain why medications have not become more consistently recommended for HIV-related fatigue. It may be that the symptom cluster of HIV-related fatigue and depression needs to be treated with psychosocial interventions. Given what is now known about the history of extensive childhood and adult trauma that has been experienced by many people with HIV infection, a better approach may be to intervene with the trauma and its sequelae rather than use medication. Given the strong relationship between psychosocial factors and fatigue, Jong and colleagues (2010) recommended research comparing the effect of medication (antidepressants, anxiolytics) and behavioral interventions (cognitive-behavioral therapy, relaxation therapy, graded exercise therapy) to direct the best treatment strategy.

Little is known about the adverse impact of HIV-related fatigue on economic markers. In the study by Dacosta Dibonaventura and colleagues (2012), every side effect – recall that fatigue was the most frequent side effect, reported by nearly 71% of participants – was associated with worse health status, some measure of increased work productivity loss, and/or some measure of increased health care resource use. We know that fatigue has a negative impact on medication adherence (Gay et al., 2011) and that fatigue tends to persist in the absence of intervention (Pence et al., 2009; Schifitto et al., 2011); thus, the quest for solutions to this problem take on a new urgency.

Case Study

Alan is a 46-year-old Caucasian man who presents to his private HIV specialist with a 3-month history of fatigue, weakness in the arms, and occasional joint pain. Diagnosed with HIV infection 12 years ago, Alan is a lawyer and lives with a partner in a private home, has a history of hepatitis B, drinks two drinks per weekend, and has no history of drug use. Baseline fatigue assessment reveals that he is experiencing fatigue severity rated as a 7 on a 0–10 scale, at least 4 out of 7 days a week. He is most fatigued in the morning but has periods of intensification randomly throughout the day.

Currently, he feels limited in his daily activities (being at court or with clients) and he is forced to sit down and needs to rest for periods of up to 30 minutes with the onset of an episode of fatigue. His chemistry/electrolytes are normal, hemoglobin and thyroid hormone levels are normal, liver function tests are slightly elevated, and he has normal testosterone values. Laboratory findings include a viral load of less than 50 copies/mL and a CD4+ T cell count of 625 cells/mm^3.

His current depressive symptom score on the Center for Epidemiologic Studies-Depression Scale is 20, indicating he should be screened by a mental health professional for clinical depression. He also complains of heightened anxiety when fatigue episodes begin. His daily exercise for the past month was limited to approximately 1,000–3,000 steps a day and consisted primarily of walking within his office or to and from the parking lot. Sleep patterns are irregular and he complains of difficulties staying asleep at night. His fatigue intensity score, as measured by the HRFS, classified him in the moderate intensity range, with high impairment in both mental and social functioning. Alan mentions that he has tried herbal supplements for fatigue and for better sleep in addition to his antiretroviral therapy medications.

Initial visit:

- Complete fatigue assessment using HRFS and Center for Epidemiologic Studies-Depression Scale to differentiate between fatigue and depression, and problems with activities of daily living, social functioning, and mental functioning due to fatigue.
- Collaborate with mental health provider and physical therapist in conducting an initial assessment and developing strategies to improve mental health and exercise status, taking into consideration Alan's lifestyle, preferences, and resources.
- Provide additional counseling and specific options for improved sleep routines and a sleep diary.

After 1 Week:

Alan has been ruled out for physiological causes of fatigue but meets all indicators for a mental health evaluation for the presence of major depression and anxiety disorder. In addition, his primary care provider also recommended he try a combined walking and resistance exercise (stretchy band) intervention. In order to help Alan stay motivated, his provider mentions that exercise with a training partner has proven more effective and less boring; Alan needs to increase his step count over the next 12 weeks from 1,000 to 10,000 steps.

1-month follow-up:

- Assess for recommendations of mental health provider, therapy, behavioral interventions, or medication prescriptions.
- Assess for any changes in fatigue status, focusing on mood, behaviors, tolerance of physical activity, and any new problems or barriers. If no improvement, screen for stress level, conflict in relationship, frequent travels, and other potential fatigue etiologies.
- Evaluate effectiveness of physical therapy and level of step count.
- Inquire about acceptance of individual counseling sessions.
- Collaborate with Alan and his partner, health care team members, and others to develop strategies to address sleep, maintaining work, reduction of stressors, and other issues.

3-month follow-up:

- Alan reports that with the help of some antidepressants, the support of his counselor, and a daily walk around the local lake, his fatigue has decreased in frequency and severity. He is satisfied with his sleep (without sleep aids) and talks about his improved relationship with his partner since they started walking together. He is much more satisfied with his work performance since he asked his company to reduce some of his client load while he is getting better.

Clinical Considerations

- Fatigue remains the most problematic and frequently occurring symptom for people with HIV infection.
- Nurses need to assess for fatigue, preferably using a valid and reliable tool.
- The factors that should be ruled out first as a potential cause of fatigue include anemia and hypogonadism; the nurse should facilitate getting these tests done.
- However, all lab work may be normal. Stress, with its attendant anxiety and depression, seems to be the most consistent predictor of HIV-related fatigue.
- The nurse should assess for depression as a treatable cause of fatigue.
- One of the most useful nursing interventions is to have the patient track fatigue over time in a diary; this helps him/her determine what patterns exist in order to better plan activities.

Disclosures

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References

Aaronson, L. S., Teel, C. S., Cassmeyer, V., Neuberger, G. B., Pallikkathayil, L., Pierce, J., … Wingate, A. (1999). Defining and measuring fatigue. *IMAGE: Journal of Nursing Scholarship*, *31*, 45-50. http://dx.doi.org/10.1111/j.1547-5069.1999.tb00420.x

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders*. text revision (4th edition). Washington, DC: Psychiatric Press, Inc.

Aouizerat, B. E., Miaskowski, C. A., Gay, C., Portillo, C. J., Coggins, T., Davis, H., … Lee, K. A. (2010). Risk factors and symptoms associated with pain in HIV-infected adults. *Journal of the Association of Nurses in AIDS Care*, *21*, 125-133. http://dx.doi.org/10.1016/j.jana.2009.10.003

Barroso, J. (2001). "Just worn out": A qualitative study of HIV-related fatigue. In S. G. Funk, E. M. Tornquist, & J. Leeman (Eds.), *Key aspects of preventing and managing chronic illness* (pp. 183-194). New York, NY: Springer.

Barroso, J., Carlson, J. R., & Meynell, J. (2003). Physiological and psychological markers associated with HIV-related fatigue. *Clinical Nursing Research*, *12*, 49-68. http://dx.doi.org/10.1177/1054773803238740

Barroso, J., Hammill, B. G., Leserman, J., Salahuddin, N., Harmon, J. L., & Pence, B. W. (2010). Physiological and psychosocial factors that predict HIV-related fatigue. *AIDS and Behavior*, *14*, 1415-1427. http://dx.doi.org/10.1007/s10461-010-9691-2

Barroso, J., & Lynn, M. R. (2002). Psychometric properties of the HIV-Related Fatigue Scale. *Journal of the Association of Nurses in AIDS Care*, *13*, 66-75. http://dx.doi.org/10.1016/S1055-3290(06)60242-2

Barroso, J., Preisser, J. S., Leserman, J., Gaynes, B. L., Golden, R. N., & Evans, D. L. (2002). Predicting fatigue and depression in HIV-positive gay men. *Psychosomatics*, *43*, 317-325.

Bormann, J., Shively, M., Smith, T. L., & Gifford, A. L. (2001). Measurement of fatigue in HIV-positive adults: Reliability and validity of the Global Fatigue Index. *Journal of the Association of Nurses in AIDS Care*, *12*, 75-83. http://dx.doi.org/10.1016/S1055-3290(06)60146-5

Breitbart, W., McDonald, M. V., Rosenfeld, B., Monkman, N. D., & Passik, S. (1998). Fatigue in ambulatory AIDS patients. *Journal of Pain and Symptom Management*, *15*, 159-167. http://dx.doi.org/10.1016/S0885-3924(97)00260-1

Breitbart, W., Rosenfeld, B., Kaim, M., & Funesti-Esch, J. (2001). A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. *Archives of Internal Medicine*, *161*, 411-420. http://dx.doi.org/10.1001/archinte.161.3.411

Cook, P. F., Sousa, K. H., Matthews, E. E., Meek, P. M., & Kwong, J. (2011). Patterns of change in symptom clusters with HIV disease progression. *Journal of Pain and Symptom Management*, *42*, 12-23. http://dx.doi.org/10.1016/j.jpainsymman.2010.09.021

Corless, I. B., Bunch, E. H., Kemppainen, J. K., Holzemer, W. L., Nokes, K. M., Eller, L. S., … Chou, F. Y. (2002). Self-care for fatigue in patients with HIV. *Oncology Nursing Forum*, *29*, E60-E69. http://dx.doi.org/10.1188/02.ONF.E60-E69

Currier, J., Lazzarin, A., Sloan, L., Clumeck, L., Slims, J., McCarty, D., … Millard, J. (2008). Antiviral activity and safety of aplaviroc with lamivudine/zidovudine in HIV-infected, therapy naïve patients: The ASCENT (CCR 102881) study. *Antiviral Therapy*, *13*, 297-306.

Dacosta Dibonaventura, M., Gupta, S., Cho, M., & Mrus, J. (2012). The association of HIV/AIDS treatment side effects with health status, work productivity, and resource use. *AIDS Care*, *24*(6), 744-755. http://dx.doi.org/10.1080/09540121.2011.630363

Darko, D. F., McCutchan, J. A., Kripke, D. F., Gillin, J. C., & Golshan, S. (1992). Fatigue, sleep disturbance, disability, and indices of progression of HIV infection. *American Journal of Psychiatry*, *149*, 514-520.

Derry, D. M. (1996). Thyroid hormone therapy in patients infected with human immunodeficiency virus: A clinical approach to treatment. *Medical Hypotheses*, *47*, 227-233. http://dx.doi.org/10.1016/S0306-9877(96)90085-7

Editors of the American Heritage Dictionaries. Fatigue. In The American Heritage® Stedman's Medical Dictionary. Retrieved from http://dictionary.reference.com/browse/fatigue

Ferrando, S., Evans, S., Goggin, K., Sewell, M., Fishman, B., & Rabkin, J. (1998). Fatigue in HIV illness: Relationship to depression, physical limitations, and disability. *Psychosomatic Medicine*, *60*, 759-764.

Fukunishi, I., Hosaka, T., Matsumoto, T., Hayashi, M., Negishi, M., … Moriya, H. (1997). Liaison psychiatry and HIV infection (II): Application of relaxation in HIV positive patients. *Psychiatry and Clinical Neurosciences*, *51*, 5-8. http://dx.doi.org/10.1111/j.1440-1819.1997.tb02358.x

Gay, C., Portillo, C. J., Kelly, R., Coggins, T., Davis, H., Aouizerat, B. E., … Lee, K. A. (2011). Self-reported medication adherence and symptom experience in adults with HIV. *Journal of the Association of Nurses in AIDS Care*, *22*, 257-268. http://dx.doi.org/10.1016/j.jana.2010.11.004

Henderson, M., Safa, F., Easterbrook, P., & Hotopf, M. (2005). Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy. *HIV Medicine*, *6*, 347-352. http://dx.doi.org/10.1111/j.1468-1293.2005.00319.x

Holzemer, W. L. (2002). HIV and AIDS: The symptom experience. *American Journal of Nursing*, *102*(4), 48-52. http://dx.doi.org/10.1097/00000446-200204000-00023

Honn, V. J., & Bornstein, R. A. (2002). Social support, neuropsychological performance, and depression in HIV infection. *Journal of International Neuropsychological Society*, *8*, 436-447. http://dx.doi.org/10.1017/S1355617702813236

Jong, E., Oudhoff, L. A., Epskamp, C., Wagener, M. N., van Duijn, M., Fischer, S., & van Gorp, E. C. (2010). Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. *AIDS*, *24*, 1387-1405. http://dx.doi.org/10.1097/QAD.0b013e328339d004

Jordan, W. C. (1998). The effectiveness of intermittent hyperbaric oxygen in relieving drug-induced HIV-associated neuropathy. *Journal of the National Medical Association*, *90*, 355-358.

Justice, A. C., Rabeneck, L., Hays, R. D., Wu, A. W., & Bozzette, S. A. (1999). Sensitivity, specificity, reliability, and clinical validity of provider-reported symptoms: A comparison with self-reported symptoms. *Journal of Acquired Immune Deficiency Syndromes*, *21*, 126-133.

Kudel, I., Cotton, S., Szaflarski, M., Holmes, W. C., & Tsevat, J. (2011). Spirituality and religiosity in patients with HIV: A test and expansion of a model. *Annals of Behavioral Medicine*, *41*, 92-103. http://dx.doi.org/10.1007/s12160-010-9229-x

Lee, K. A., Gay, C., Portillo, C. J., Coggins, T., Davis, H., Pullinger, C. R., & Aouizerat, B. E. (2012). Types of sleep problems in adults living with HIV/AIDS. *Journal of Clinical Sleep Medicine*, *8*, 67-75.

Lee, K. A., Portillo, C. J., & Miramontes, H. (1999). The fatigue experience for women with human immunodeficiency virus. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, *28*, 193-200. http://dx.doi.org/10.1111/j.1552-6909.1999.tb01984.x

Lerdal, A., Gay, C. L., Aouizerat, B. E., Portillo, C. J., & Lee, K. A. (2011). Patterns of morning and evening fatigue among adults with HIV/AIDS. *Journal of Clinical Nursing*, *20*, 2204-2216. http://dx.doi.org/10.1111/j.1365-2702.2011.03751.x

Leserman, J., Barroso, J., Pence, B. W., Salahuddin, N., & Harmon, J. L. (2008). Trauma, stressful life events, and depression predict HIV-related fatigue. *AIDS Care*, *20*, 1258-1265. http://dx.doi.org/10.1080/09540120801919410

Low, Y., Preud'homme, X., Goforth, H. W., Omonuwa, T., & Krystal, A. D. (2011). The association of fatigue with depression and insomnia in HIV-seropositive patients: A pilot study. *Sleep*, *34*, 1723-1736. http://dx.doi.org/10.5665/sleep.1446

McElhiney, M., Rabkin, J., Van Gorp, W., & Rabkin, R. (2010). Modafinil effects on cognitive function in HIV+ patients treated for fatigue: A placebo controlled study. *Journal of Clinical and Experimental Neuropsychology*, *32*, 474-480. http://dx.doi.org/10.1080/13803390903201769

Millikin, C. P., Rourke, S. B., Halman, M. H., & Power, C. (2003). Fatigue in HIV/AIDS is associated with depression and subjective neurocognitive complaints but not neuropsychological functioning. *Journal of Clinical and Experimental Neuropsychology*, *25*, 201-215. http://dx.doi.org/10.1076/jcen.25.2.201.13644

Murphy, D. A., Moscicki, A. B., Vermund, S. H., & Muenz, L. R. (2000). Psychological distress among HIV-positive adolescents in the REACH study: Effects of life stress, social support, and coping. *Journal of Adolescent Health*, *27*, 391-398. http://dx.doi.org/10.1016/S1054-139X(00)00158-0

Paddison, J., Fricchione, G., Ghandi, R. T., & Freudenreich, O. (2009). Fatigue in psychiatric HIV patients: A pilot study of psychological correlates. *Psychosomatics*, *50*, 455-460. http://dx.doi.org/10.1016/S0033-3182(09)70837-0

Payne, C., Whiffen, P. J., & Martin, S. (2012). Interventions for fatigue and weight loss in adults with advanced progressive illness. *Cochrane Database of Systematic Reviews*, *1*. http://dx.doi.org/10.1002/14651858.CD008427.pub2. Art. No.: CD008427.

Pence, B. W., Barroso, J., Harmon, J. L., Leserman, J., Salahuddin, N., & Hammill, B. G. (2009). Chronicity and remission of fatigue in patients with established HIV infection. *AIDS Patient Care and STDs*, *23*, 239-244. http://dx.doi.org/10.1089/apc.2008.0175

Pence, B. W., Barroso, J., Leserman, J., Harmon, J. L., & Salahuddin, N. (2008). Measuring fatigue in people living with HIV/AIDS: Psychometric characteristics of the HIV-Related Fatigue Scale. *AIDS Care*, *20*, 829-837. http://dx.doi.org/10.1080/09540120701694063

Perkins, D. O., Leserman, J., Stern, R. A., Baum, S. F., Liao, D., Golden, R. N., & Evans, D. L. (1995). Somatic symptoms and HIV infection: Relationship to depressive symptoms and indicators of HIV disease. *American Journal of Psychiatry*, *152*, 1776-1781.

Phillips, K. D., Sowell, R. L., Rojas, M., Tavakoli, A., Fulk, L. J., & Hand, G. A. (2004). Physiological and psychological correlates of fatigue in HIV disease. *Biological Research for Nursing*, *6*, 59-74. http://dx.doi.org/10.1177/1099800404264846

Rabkin, J. G., Ferrando, S. J., Wagner, G. J., & Rabkin, R. (2000). DHEA treatment for HIV+ patients: Effects on mood, androgenic and anabolic parameters. *Psychoneuroendocrinology*, *25*, 53-68. http://dx.doi.org/10.1016/S0306-4530(99)00036-0

Rabkin, J. G., McElhiney, M. C., & Rabkin, R. (2011a). Modafinil and armodafinil treatment for fatigue in HIV-positive patients with and without chronic hepatitis C. *International Journal of STD and AIDS*, *22*, 95-101.

Rabkin, J. G., McElhiney, M. C., & Rabkin, R. (2011b). Treatment of HIV-related fatigue with armodafinil: A placebo-controlled randomized trial. *Psychosomatics: Journal of Consultation Liaison Psychiatry*, *52*, 328-336. http://dx.doi.org/10.1016/j.psym.2011.02.005

Rabkin, J. G., McElhiney, M. C., Rabkin, R., & Ferrando, S. J. (2004). Modafinil treatment for fatigue in HIV+ patients. *Journal of Clinical Psychiatry*, *65*, 1688-1695. http://dx.doi.org/10.4088/JCP.v65n1215

Rabkin, J. G., McElhiney, M. C., Rabkin, R., & McGrath, P. J. (2010). Modafinil treatment for fatigue in HIV/AIDS: A randomized placebo-controlled study. *Journal of Clinical Psychiatry*, *71*, 707-715. http://dx.doi.org/10.4088/JCP.09m05171bro

Rabkin, J. G., Wagner, G. J., & Rabkin, R. (2000). A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Archives of General Psychiatry*, *57*, 141-147. http://dx.doi.org/10.1001/archpsyc.57.2.141

Ream, E., & Richardson, A. (1996). Fatigue: A concept analysis. *International Journal of Nursing Studies*, *33*, 519-529. http://dx.doi.org/10.1016/0020-7489(96)00004-1

Reillo, M. R. (1993). Hyperbaric oxygen therapy for the treatment of debilitating fatigue associated with HIV/AIDS. *Journal of the Association of Nurses in AIDS Care*, *4*, 33-38.

Roberts, J. E., Ciesla, J. A., Direnfeld, D. M., & Hewitt, R. G. (2001). Emotional distress among HIV-positive individuals: The roles of acute negative life events and psychological diatheses. *Personal and Individual Differences*, *30*, 241-257. http://dx.doi.org/10.1016/S0191-8869(00)00042-8

Safren, S. A., Hendriksen, E. S., Smeaton, L., Celentano, D. D., Hosseinipor, M. C., Barnett, L., … Campbell, T. (2012). Quality of life among individuals with HIV starting antiretroviral therapy in diverse resource-limited areas of the world. *AIDS and Behavior*, *16*, 266-277. http://dx.doi.org/10.1007/s10461-011-9947-5

Schifitto, G., Deng, L., Yeh, T. M., Evans, S. R., Ernst, T., Zhong, J., & Clifford, D. (2011). Clinical, laboratory, and neuroimaging characteristics of fatigue in HIV-infected individuals. *Journal of Neurovirology*, *17*, 17-25. http://dx.doi.org/10.1007/s13365-010-0010-5

Sewell, M. C., Goggin, K. J., Rabkin, J. G., Ferrando, S. J., McElhiney, M. C., & Evans, S. (2000). Anxiety syndromes and symptoms among men with AIDS. *Psychosomatics*, *41*, 294-300.

Siegel, K., Brown-Bradley, C. J., & Lekas, H. M. (2004). Strategies for coping with fatigue among HIV-positive individuals fifty years and older. *AIDS Patient Care & STDs*, *18*, 275-288. http://dx.doi.org/10.1089/108729104323076016

Simmonds, M. J., Novy, D., & Sandoval, R. (2005). The differential influence of pain and fatigue on physical performance and health status in ambulatory patients with human immunodeficiency virus. *Clinical Journal of Pain*, *21*, 200-206.

Smith, B. A., Neidig, J. L., Nickel, J. T., Mitchell, G. L., Para, M. F., & Fass, R. J. (2001). Aerobic exercise: Effects on parameters related to fatigue, dyspnea, weight and body composition in HIV-infected adults. *AIDS*, *15*, 693-701. http://dx.doi.org/10.1097/00002030-200104130-00004

Sullivan, P., & Dworkin, M. S. (2003). Prevalence and correlates of fatigue among persons with HIV infection. *Journal of Pain and Symptom Management*, *25*, 329-333. http://dx.doi.org/10.1016/S0885-3924(02)00676-0

Vlahov, D., Munoz, A., Solomon, L., Astemborski, J., Anderson, J., Galai, N., & Nelson, K. E. (1994). Comparison of clinical manifestations of HIV disease between male and female injecting drug users. *AIDS*, *8*, 819-823. http://dx.doi.org/10.1097/00002030-199406000-00015

Vogl, D., Rosenfeld, B., Breitbart, W., Thaler, H., Passik, S., McDonald, M., & Portenoy, R. K. (1999). Symptom prevalence, characteristics, and distress in AIDS outpatients. *Journal of Pain and Symptom Management*, *18*, 253-262. http://dx.doi.org/10.1016/S0885-3924(99)00066-4

Voss, J. G. (2005). Predictors and correlates of fatigue in HIV/AIDS. *Journal of Pain and Symptom Management*, *29*, 173-184. http://dx.doi.org/10.1016/j.jpainsymman.2004.05.006

Voss, J. G., Dobra, A., Morse, C., Kovacs, J. A., Raju, R., Danner, R. L., … Dalakas, M. (2011). Fatigue-related gene networks in $CD14^+$ cells isolated from HIV infected patients – Part II: Statistical analysis. [Nov 14 Epub ahead of print]. *Biological Research for Nursing.* http://dx.doi.org/10.1177/1099800411423307

Wagner, G. J., & Rabkin, R. (2000). Effects of dextroamphetamine on depression and fatigue in men with HIV: A double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*, *61*, 436-440. http://dx.doi.org/10.4088/JCP.v61n0608

Wagner, G. J., Rabkin, J. G., & Rabkin, R. (1998). Testosterone as a treatment for fatigue in HIV+ men. *General Hospital Psychiatry*, *20*, 209-213. http://dx.doi.org/10.1016/S0163-8343(98)00024-3

Walker, K., McGown, A., Jantos, M., & Anson, J. (1997). Fatigue, depression, and quality of life in HIV-positive men. *Journal of Psychosocial Nursing and Mental Health Services*, *35*, 32-40.

Wantland, D. J., Mullan, J. P., Holzemer, W. L., Portillo, C. J., Bakken, S., & McGhee, E. M. (2011). Additive effects of numbness and muscle aches on fatigue occurrence in individuals with HIV/AIDS who are taking antiretroviral therapy. *Journal of Pain and Symptom Management*, *41*, 469-477. http://dx.doi.org/10.1016/j.jpainsymman.2010.05.011

Whetten, K., Reif, S., Whetten, R., & Murphy-McMillan, L. K. (2008). Trauma, mental health, distrust, and stigma among HIV-positive persons: Implications for effective care. *Psychosomatic Medicine*, *70*, 531-538.