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Predictors and correlates of fatigue in people living with HIV/AIDS

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Predictors and Correlates of Fatigue in People Living with HIV/AIDS

by

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Abstract

Predictors and Correlates of Fatigue in Persons Living with HIV/AIDS

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University of California, San Francisco, 2003

The purposes of this study were to: describe the intensity of fatigue by selected person, environment, and health/illness variables in (n=372) men and women with HIV/AIDS; to explore the potential confounding effects between fatigue and depression; and to test the UCSF Symptom Management Model (UCSF-SMM) through identifying predictors and correlates of fatigue related to physical and mental health. This study was a secondary data analysis based upon a previous descriptive survey. The sample included 63% male at a mean age of 40.3 ± 7.8 years and 32% female at a mean age of 39.5 ± 9.2 years, 73% African Americans, 15% Caucasians and 9% Latinos. Women, Hispanics, the disabled, those with inadequate income or insurance, and those who did not work for pay, reported higher fatigue intensity. Of 51% of the total sample reported moderate to severe fatigue intensity on the revised Sign and Symptom Checklist (SSC-HIVrev), and 86% of the total sample reported depressive symptoms as measured by the Center for Epidemiologic Studies-Depression total score > 15. Women rated fatigue and depression intensity factor scores higher than men on the SSC-HIVrev. The contributions of fatigue to physical and mental health within the context of the UCSF-SMM were explored through two hierarchical regression models. The physical health model explained 37.4% of the total amount of variance and fatigue explained only 2% of it. The mental health model explained 23.2% of the total amount of variance and fatigue did not make a unique contribution. Fatigue was a serious problem and occurred most likely in combination with other physical and mental symptoms. The results of this study imply the need for gender and ethnic-specific fatigue research. Longitudinal symptom cluster research is necessary to fully discover the impact that fatigue has on mental health and depression.

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Table of Contents

List of Tables

List of Figures

CHAPTER ONE

THE STUDY PROBLEM

Introduction

Worldwide, an estimated 42 million men, women and children are infected with the Human Immunodeficiency Virus (HIV), or live with the Acquired Immunodeficiency Syndrome (AIDS) (UNAIDS, December 1, 2002). The trajectory of HIV disease is accompanied by a slow destruction of the body's immune system. Specifically, the destruction of the $CD4^+$ T lymphocytes, results in numerous opportunistic infections and different types of neoplasms. Since 1996, significant progress has been made in the highly active antiretroviral treatments, also known as HAART. In North America and Western Europe, the morbidity and mortality rates of the HIV disease are becoming drastically reversed. Globally, however, the death toll has reached: 1.9 million men, 1.2 million women and 610,000 children (UNAIDS, December 1, 2002).

HIV disease and its treatments are accompanied by a wide variety of signs and symptoms that challenge patients. Among those, is fatigue. Many investigators have identified it as one of the most frequent, stressful and debilitating symptoms of the HIV/AIDS disease (Barroso, 1999; Breitbart, McDonald, Rosenfeld, Monkman, & Passik, 1998; Corless et al., 2002, Holzemer et al., 1999; Vogl et al., 1999). However, the predictors and correlates of fatigue associated with HIV/AIDS have not been explored extensively, which was one of the reasons prompting the need for this research.

There are 5 chapters devoted to the investigation of the relationships between fatigue and the correlates and predictors to physical and mental health. Chapter 1

introduces the problem, the purpose, and the significance of this study; chapter 2 provides a comprehensive overview of the fatigue literature in HIV/AIDS, and is divided into three sections: research, theoretical frameworks, and measurements. In chapter 3 the methodology is outlined, followed by the results in chapter 4, and a discussion of the research findings in chapter 5.

Statement of the Problem

In 1998, Barbara Piper, a professor of nursing, defined fatigue in HIV/AIDS as "a whole-body tiredness that persists for a month or longer, and is different from daily experiences of tiredness after a long day of work " (p. 213). There were 2 established states of fatigue: an acute state and a chronic one. The acute state was defined as the occasional mental tiredness after work, or the physical exhaustion after strenuous exercise. The chronic state was defined as the persistent physical and mental tiredness without any external influences. Winningham's research in cancer-related fatigue, showed that the increase of rest and sleep periods did not resolve the chronic fatigue. Instead, it often had a negative effect on the cancer patients, which prompted Winningham to define it as a secondary fatigue (Winningham & Barton-Burke, 2000). This secondary fatigue affected the patient mentally and physically, and led to permanent disability or a decrease of one's quality of life.

The data for this investigation was taken from a study that collected symptom information on the severity, duration, and distress on several symptom assessment tools. The researchers also collected information on self-care behaviors to manage these symptoms. Two fatigue scales, one vitality scale and three depression measures were included in the original study, and provided sufficient data for this secondary analysis.

Purpose of the Study

The purpose of this secondary analysis was to expand the knowledge base of the significance of the perceived fatigue for people living with HIV/AIDS. In a sample of 372 study participants, there were three aims:

1. To describe the intensity of fatigue as influenced by selected person, environment, and health and illness variables.
2. To explore the potential confounding of fatigue and depression through an analysis of convergent and divergent correlations and known-group differences.
3. To test the UCSF - Symptom Management Model (UCSF - SMM) by exploring the contribution of fatigue to the physical and mental health of the patients.

Significance of the Study

The prevalence rates for fatigue range from 17% to 60%, in people with HIV, and from 43% to 85% in people with AIDS (Breitbart et al., 1998; Lee, Portillo, & Miramontes, 1999; Piper, 1998; Vogl et al., 1999). Women with AIDS were more likely to report fatigue (62%) than men (49%) (Breitbart et al., 1998; Lee et al., 1999). In 1997, Singh and colleagues reported that HIV patients 35 years and older scored an average

total score of 13.6 on the Profile of Mood States (POMS), compared to patients under 35 who scored only an average of 7 on the POMS ($p = 0.003$). The older group reported higher fatigue scores, indicating a significant correlation between higher age and increased perception of fatigue (Singh, Squier, Sivek, Wagener, & Yu, 1997). Many studies confirm that fatigue is a significant predictor of decreased adherence to HAART and increased likelihood of developing drug resistance (Bean, 2001; Henry, Holzemer, Weaver, & Stotts, 1999; Ostrop, Hallett, & Gill, 2000; Molassiotis, Nahas-Lopez, Chun et al., 2002; Plosker & Noble, 1999). Fatigue also predicts a decrease in quality of life, by lowering physical and social functioning, and it contributes to the development of depression and the loss of employment (Crystal, Fleishman, Hays, Shapiro, & Bozzette, 2000).

Results from this study will confirm the previous findings of fatigue ratings in people with HIV/AIDS, by investigating the differences between men and women, different ethnic groups, economic groups, and educational backgrounds. Findings of this study will contribute to the selection of more appropriate measurement tools. And finally, this study will investigate the individual contributions of fatigue to physical and mental health in order to develop future intervention research.

CHAPTER TWO

LITERATURE REVIEW

Relevant Fatigue Research

The extensive amount of research literature regarding fatigue will be introduced in four topics. First, fatigue will be presented as a predictor variable of lower adherence to HAART and quality of life ratings. Second, study findings of demographic variables predicting fatigue will be reviewed. Third, possible causal relationships will be reviewed in relation to fatigue: hematological changes, hormonal imbalances, activity or sleep patterns and psychological problems.

Fatigue as a Predictor of Adherence and Quality of Life

Predictor variables are defined to be independent variables that predict the value of the dependent variable (Polit, 1996). They should be highly correlated with the dependent variable, but not with the other independent variables. When entering fatigue as an independent variable and adherence behaviors as a dependent variable, evidence was established that increasing fatigue predicted lower adherence levels to HAART (Bean, 2001; Henry, Holzemer, Weaver, & Stotts, 1999; Ostrop, Hallett, & Gill, 2000; Molassiotis, Nahas-Lopez, Chun et al., 2002, Plosker & Noble, 1999). In 1995, Bailey and colleagues postulated that the ability to adhere could be considered a multi-factorial, complex process that would include psychosocial, client and healthcare provider issues (Bailey, Ferguson, & Voss, 1995). This was an important finding because it considered

the fact that insufficient adherence to HAART resulted in viral resistance, treatment failure and higher levels of mortality and morbidity (Easterbrook et al., 1996; Sterling et al., 2001). Fatigue was identified as one of the most frequent reasons a patient forgot to take prescribed medication doses or overslept the scheduled time for taking the medication. Fatigue was also identified as one of the contributors to the psychological resistance in medication adherence (Ostrop, Hallett, & Gill, 2000). In 1999, Proctor, Tesfa, and Tompkins conducted a study in Long Island, New York to investigate possible barriers in adherence to HAART in 39 people with HIV/AIDS. They utilized 5 focus groups with 6 to 13 participants in each, and they classified the responses into eight common barriers to medication adherence:

- frequency and severity of side effects (including fatigue)
- conflicts with daily routines
- dietary requirements
- frequency of taking medications
- number and dosage of medications
- psychosocial factors (i.e., stress, feeling good, and bad news)
- pharmacy refills
- physiological needs (i.e., sleep, hunger, or thirst)

Additional factors were identified in the success or failure of HAART, including pre-existing drug resistance, drug-drug interactions and the ability of people with HIV/AIDS to adhere to a rigid and frequently changing medication regimen (Proctor et al., 1999). Side effects, including fatigue, were one of the major obstacles for sufficient adherence regardless of gender, IV-drug use, age, educational background and economical status

(Gao, Nau, Rosenbluth, Scott, & Woodward, 2000; Proctor et al., 1999; Roberts, 2000; Roberts & Mann, 2000; Zorrilla, 2000).

In previous investigations, the increase or decrease of fatigue ratings predicted higher and lower levels of quality of life. In 1998, Cohen and colleagues conducted a randomized clinical trial with ritonavir (Protease Inhibitor) (n = 1090). They compared two groups from baseline to six months, and discovered that the ritonavir-treated group reported fewer declines in physical functioning (baseline M= -3.2 to 6 month -7.8, $p < .005$) and perceived themselves to be healthier ($p < .001$). They reported they had higher energy levels (baseline M= -1.7 to 6 month -7.8, $p < .001$), better cognitive functioning (baseline M= -0.7 to 6 month 3.8, $p = .008$) and better psychological well being (baseline M= -1.6 to 6 month -5.2, $p < .005$) than the control patients (Cohen, Revicki, Nabulsi, Sarocco, & Jiang, 1998).

Perceptions of health-related quality of life were investigated in a Swedish sample of 55 women and 134 men infected with HIV. Higher age significantly contributed to more anxiety and less energy in men, but not in women. When age was entered in a multiple regression model as the independent variable, higher age in men contributed significantly to the lower levels of energy, while holding constant disease stage, social integration, disclosure and sense of coherence ($p = 0.05$) (Cederfjall, Langius-Eklof, Lidman, & Wredling, 2001).

Molassiotis and colleagues (2001) assessed quality of life (QOL), coping-styles, mood and uncertainty, in a cross-sectional study of a non-random sample of 46 symptomatic HIV patients in Hong Kong. In the regression model, QOL was predicted

with the combined effects of illness uncertainty and fatigue (adjusted $R^2 = 0.51$, $p < 0.001$) (Molassiotis, Callaghan, Twinn, & Lam, 2001).

Increased pain and fatigue symptom intensity are strongly associated with physical and role limitations. The relationship between physical functioning and role functioning was assessed in 2,836 HIV-infected men and women who took part in the HIV Cost and Services Utilization Survey (Crystal, Fleishman, Hays, Shapiro, & Bozzette, 2000). Limitations in role functioning were more prevalent than in physical functioning. Major limitations were observed in being an employee, performing household chores or being a full-time student. In physical tasks, the limitations occurred in more energy-demanding activities, such as climbing stairs (43%) or walking more than one block (26%) than in self-care tasks, such as bathing and dressing (14%). Greater limitations in physical functioning were associated with age (>50 years), educational attainment (graduation from college), more advanced disease (CD4+ counts <200 and AIDS diagnosis) and higher symptom burden. Breitbart and colleagues (1998), Cunningham and colleagues (1998), and Darko, Mitler and Henriksen (1995), presented similar results in their studies.

Demographic variables such as age, gender and ethnicity are influenced by perception of symptoms. In a sample of 427 ambulatory men and women with AIDS, Breitbart and colleagues (1998) reported that 61.6% of the women had fatigue, compared to 50% of the men ($\chi^2 = 5.28$, $p = 0.03$). Ethnicity did not predict significant differences in fatigue, with 55.1% of the Caucasians compared to 53.5% of the non-Caucasians reporting fatigue. Sexual orientation was a significant predictor of fatigue, with 37.8% of homosexuals reporting the lowest fatigue, compared to intravenous drug users with

(59.5%) and heterosexuals (58.2%) (χ^2 = 7.72, p = 0.03) (Breitbart et al., 1998). The relationship between fatigue and age or years of education was not statistically significant in this sample.

Lee, Portillo and Miramontes (1999) conducted a study with 100 HIV-infected women. European-American women reported higher evening fatigue scores (range 60.0 ± 17.7) than African-American (46.1 ± 20.4) and Hispanic women (43.4 ± 16.3). Higher income and European-American ethnicity explained 51% of the variance in the evening fatigue (F = 5.0, p = 0.006).

Increasing levels of fatigue predicted non-adherence behaviors and lower quality of life. In many studies, fatigue increased with the number of symptoms and further progression of the disease status. Perception of fatigue showed inconclusive results for some of the demographic variables. Potentially, this could be an attribute of cultural differences of what symptom would be acceptable to perceive and report. Women in most cultures were more likely to discuss vulnerabilities, and thus, report their symptoms. It is not known whether health disparities, such as homelessness, reduced access to healthcare or care received through a health maintenance organization would predict fatigue for different HIV populations.

Potential Correlates of Fatigue

Researchers have investigated a number of potential causal relationships between HIV disease, fatigue and HAART. The section was divided into four sub-sections: hematological changes, hormonal imbalances, activity/sleep patterns, and psychological problems.

Hematological Changes

Anemia is the most common hematological abnormality in patients with HIV/AIDS (Groopman, 1998; Henry, 1998, Moyle, 2002). Fatigue is a frequent symptom of anemia because of insufficient amounts of erythrocytes and their subsequent inability to deliver oxygen to the mitochondria (Schultz & Freedman, 1987). Mitochondria are the cell organelles that generate most of the energy for all the body functions; a process known as oxidative phosphorylation (Winningham & Barton-Burke, 2000; Moyle, 2002). Anemia occurs in 66% to 85% of all people with HIV. The majority suffers from a chronic disease-type anemia, with low reticulocyte counts and low erythropoetin levels (Spivak, Barnes, Buchs, & Quinn, 1989). Anemia in HIV/AIDS is a complex and multicausal disease, and is explained by contributing factors, including myelosuppression through chemotherapeutic agents (e.g. zidovudine), infections of the bone marrow with opportunistic infections and malignancies, and by the effects of the HIV virus on the bone marrow and haemopoiesis (Evans & Scadden, 2000). Anemia is a prognostic marker for future disease progression or death, independent of CD4+ cell count or viral load (Moyle, 2002). Ambiguous relationships were reported for fatigue and CD4+ cell counts. In subjects with AIDS-related complex (ARC), Darko and colleagues (1992) found higher levels of fatigue than in asymptomatic subjects and those with end-stage disease (Darko, McCutchan, Kripke, Gillin, & Golshan, 1992). Lubeck and Fries (1993) and Walker, McGown, Jantos and Anson (1997) found similar results. They concluded that with disease progression and lower CD4+ counts, the level of fatigue increases (Lubeck & Fries, 1993; Walker et al., 1997). However, the relationships between the

stage of disease and the ratings of fatigue were not confirmed in later studies (Breitbart et al., 1998; Cederfjall et al., 2001; Lee et al., 1999). The broad availability of HAART, in 1996, could be the possible explanation for the changing symptom and disease stage patterns. Prior to that, the progression from HIV to AIDS was accompanied by multiple opportunistic infections. These caused patients to loose muscle and fat mass, as well as experience general weakness and limited mobility due to frequent hospitalizations (secondary fatigue). With the advancements of therapies, the sharp declines in CD4+ cells are not observed as frequently. HAART improves patients' lives significantly and stabilizes the loss of CD4+ cells. The relationship of CD4+ cells to fatigue has never been based on the most reliable data. Over the course of 24 hours, CD4+ cell counts fluctuate widely (between 150-300), which make them less reliable physiological markers. In addition, from a fatigue perspective, the energy that CD4+ cells produce is mainly utilized for their own function. The mitochondria in CD4+ cells do not contribute to the energy needs of other cells. Therefore, the early findings between the higher fatigue ratings and lower CD4 + counts, are most likely attributable to the tiring effects of infections and the treatments. Aside from CD4+ cell counts, viral load has become the new focal point in monitoring the effectiveness of HAART and HIV/AIDS disease progression. However, correlations between viral load and fatigue are not statistically significant (Breitbart et al., 1998, Barroso, Carlson & Meynell, 2003).

Hormonal Imbalances and Fatigue

A number of investigators found testosterone replacement therapy to be an effective treatment for fatigue. Testosterone replacement is well tolerated and it is an

effective short-term treatment of clinical hypogonadism. In men with HIV/AIDS, it restores libido and energy, alleviates depressed mood, and increases muscle mass (Capaldini, 1998; Ferrando, Rabkin, & Poretsky, 1999; Ferrando, Wagner, & Rabkin, 2000; Rabkin, Wagner, & Rabkin, 2000; Wagner & Rabkin, 1998; Wagner, Rabkin, & Rabkin, 1998).

Findings of endocrine dysfunction of the gonads and other glands are quite frequent in people with HIV/AIDS. This review focuses on testosterone deficiency. Testosterone is responsible for the regulation of normal growth, bone metabolism and body composition. Men and women with testosterone deficiency have changes in body composition, including the increase in body fat and loss of lean muscle mass. Quantitative CT scans revealed a relationship between testosterone deficiency and fat distribution, showing increasing adipose depositions in all areas of the body, particularly in the subcutaneous and muscle areas (Renard, Fabre, Paris, Reynes, & Bringer, 1999). Testosterone deficiency might have important implications to overall health, morbidity and mortality. The increase in truncal fat deposits correlates with the occurrence of glucose intolerance and cardiovascular risk. Potentially, it causes HIV patients to develop diabetes and myocardial infarctions. Furthermore, testosterone deficiency is associated with an enhanced risk for osteoporosis and decreased muscle performance (Bashin, Woodhouse, & Storer, 2001). Fatigue is one of the leading symptoms of testosterone deficiency and hypogonadism (Rabkin, Wagner, & Rabkin, 2000). Microscopic investigations of gonads show a decrease in spermatogenesis, thickening of the tunica propria, mild to moderate interstitial infiltrates and/or fibrosis (De Paepe & Waxman, 1989). Dobs and colleagues (1996) found decreased libido in 28 of 42 men with AIDS,

with 14 patients reporting impotence. In 45% of the sample, free testosterone levels were subnormal, yet in most of the men, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were not elevated. The response to stimulation with gonadotropin-releasing hormone was mostly normal (Dobs et al., 1996). These findings indicate that the observed hypogonadism is due to a functional disorder of the hypothalamus and a lack of gonadotropin-releasing hormone release (Schambelan & Grunfeld, 1999).

Reduced androgen levels are also observed in women with HIV/AIDS. Recent data suggest that the testosterone deficiency in women is due to altered androgen metabolism (Huang et al., 2003). Total and free testosterone levels of 69 HIV-infected women were compared to 25 healthy women. Both testosterone levels were significantly reduced, however, the HIV-infected women were more inclined to weight loss greater than 10% (OR= 3.5, CI= not available, N= 85, p= .04) than the healthy women. (Huang, et al., 2003).

Activity and Sleep Patterns and Fatigue

Researchers have proposed relationships between fatigue and increased Resting Energy Expenditure (REE) in patients with HIV/AIDS (Lane & Provost-Craig, 2000; Salomon, de Truchis, & Melchior, 2002; Batterham, et al., 2003). It was proposed that up-regulation of energy expenditure caused patients to feel more tired and exhausted than their healthy counterparts. Also, REE was thought to be the causal explanation of the wasting syndrome in HIV/AIDS patients. They reported fatigue as one of their major limiting symptoms with clinical symptoms of weight loss and higher REE. Lane and Provost-Craig (2000) studied the REE differences in 26 HIV-infected women and 16

healthy women. They found statistically significant differences ($p < 0.05$) in the HIV-infected women when adjusting for body composition. REE was 17% higher in the HIV-positive group (1755 ± 410 kcal/kg), compared to the control group (1497 ± 197 kcal/kg).

Elevated REE in HIV/AIDS patients can be explained by the elevation of certain cytokines, especially tumor necrosis factor alpha (TNF-α). TNF-α is a cytokine, mainly produced by activated phagocytes. It stimulates the recruitment of neutrophils and monocytes to sites of infection, and it activates these cells to eradicate microbes. In severe infections, TNF-α is produced in large quantities and has systemic effects. They cause symptoms, including fatigue, fever, cachexia or synthesis of acute phase proteins by the liver. Results of Lane and Provost-Craig (2000) revealed 17% higher levels of TNF-α in the HIV-positive subjects ($p < 0.01$); however, a weak correlation was found between TNF-α and REE ($r= 0.35$).

Pernerstorfer-Schoen and colleagues (1999) investigated the effects of HAART on REE. HIV/AIDS patients treated with HAART had elevated REE compared to the controls at baseline. The treatment with HAART decreased REE in HIV/AIDS patients on regimen containing protease inhibitors (PI) ($p < 0.05$). A reduction in the viral burden preceded the decrease in REE by several weeks (Pernerstorfer-Schoen et al., 1999). Shevitz and colleagues (1999) analyzed a cohort of HIV patients and found that the amount of HIV RNA in the plasma was directly correlated with REE. There was significant increase in REE of 90 kJ/day per log 10 copies/ml with an increase in HIV RNA (95% confidence interval (CI) 16-164; $p < 0.02$), adjusting for fat mass, age, CD4+ cell count and HAART use. HAART use had an independent effect on REE. It was 339 kJ/day higher in the patients who reported HAART use than in those who did not (95%

CI 177-501; $p < 0.001$) (Shevitz et al., 1999). These results suggest that patients treated with HAART potentially experience higher levels of fatigue.

Sleep disturbances are common in HIV/AIDS patients, which lead to decreased energy, increased rest patterns and more fatigue (Nokes & Kendrew, 1996, 2001). Perception of fatigue can be explained by the lack of sleep or by the development of a secondary fatigue. The secondary fatigue can be triggered by excessive sleep with no qualitative difference in the perception of rest for the individual. Vogl and colleagues (1999), reported high prevalence rates for sleep disturbances: 73.8% of their 504 outpatients with AIDS reported poor sleep, of which 58.5% reported it to be highly stressful (Vogl et al., 1999). Causal explanations for sleep disturbances included HIV-related symptoms such as fever, diarrhea, and night sweat or side effects from HAART and anti-depressants. However, there were many other factors, that contribute to the development of sleep disturbances: HIV infection of the brain and the nervous system, opportunistic infections, neoplasm associated with the HIV disease or social and environmental factors such as a difficult housing situations, hospitalization, or limited income (Cohen et al., 1996).

Sleep is divided into five sleep stages: rapid eye movement sleep (REM), and four stages of non-REM (NREM) sleep. Stages 3 and 4 of NREM sleep is known as slow wave sleep or delta sleep, and is characterized as the deep and restorative sleep (White et al., 1995). HIV-related fatigue might be promoted by regulatory cytokines, which are increased in HIV infection. These cytokines have somnogenic effects and induce NREM sleep (Darko et al., 1992; Darko, Miller, Gallen, et al., 1995; Darko, Mitler, & White, 1995). In particular, TNF-α produces significant dose-dependent increases in NREM

sleep when injected into rabbits intravenously (Shoham, Davenne, Cady, Dinarello, & Krueger, 1987). A treatment for fatigue and similar distressful symptoms could be a TNF-α antagonist (Odeh, 1990).

Indirect evidence supports the relationship between increased NREM sleep, fatigue and depressive symptoms in chronic illnesses (Olders & Winningham, 2000). Olders and Winningham (2000) argue that ill people spent more time in bed (Guilleminault & Moldini, 1986), citing examples of cancer patients receiving treatments (Greenberg, Gray, Mannix, Eisenthal, & Carey, 1993). They argue further, that by increasing the hours of daytime rest, physical fatigue increases as a result of the additional rest and deconditioning (Graydon, Bubela, Irvine, & Vincent, 1995; Kobashi-Schoot, Hanewald, van Dam, & Bruning, 1985). Finally, increasing fatigue would lead the patients to rest even more (Dodd, 1984) and excessive inactivity would lead to insomnia (Spielman, Saskin, & Thorpy, 1987), which was a frequent observation in cancer patients with fatigue (Degner & Sloan, 1995).

Psychological Problems and Fatigue

In HIV disease, fatigue is considered a cause of depression (Perkins et al., 1995). Fatigue is also considered to be one of the primary symptoms of depression (Breitbart, Rosenfeld, Kaim, & Funesti-Esch, 2001, Lipsitz et al., 1994). In the early days of the HIV/AIDS epidemic, it was difficult to separate the two concepts. Different methods and instruments have been used in the last 10 years to achieve a better conceptual distinction (Breitbart et al., 2001; Rabkin, 2001).

Recent studies refute earlier findings of markedly higher prevalence rates (50% and higher) of depression in people with HIV disease (Atkinson et al., 1988; Judd & Mijch, 1994; Lipsitz et al., 1994; Rabkin & Gewirtz, 1992). Standardized depression-rating scales are now used instead of unreliable self-report scales. They found prevalence rates for depression to range between 22% and 32% in non-drug-using HIV patients (Evans et al. 1998, Ferrando et al, 1998), compared to approximately 17% in the general population (Blazer, Kessler, McGonagle, & Swartz, 1994). Challenging drug therapies, limiting side effects and the perspective of being chronically ill, are some of the many stressors of depression in HIV patients. Specific stressors include prolonged periods of physical discomfort, disability, dependence, lifestyle changes, loss of employment and steady income, disruption of social networks, and decrease in self-esteem. Treatments for HIV disease, as well as other medications, might have been a cause of depression (Morris, 1994).

Depressive symptoms consistently correlated with physical symptom reports (Rabkin & Klein, 1987). The clinical overlap between physical symptoms of HIV infection, neuropsychological symptoms and depressive symptoms (such as fatigue, poor appetite, weight loss, and trouble concentrating), make it difficult to select the most appropriate approach for diagnosing depression.

Different approaches have been used to diagnose depression, which either include or exclude fatigue as a diagnostic criterion. Rifkin and colleagues (1985) utilize the inclusive approach and count all symptoms in making a diagnosis of depression, regardless of whether or not the symptoms could have been attributable to a physical problem (Rifkin et al., 1985).

The etiological approach by Spitzer and Wakefield (1999), developer of the Diagnostic and Statistical Manual of Mental Disorders (DSM), requires an interviewer to attribute causal somatic symptoms to depression. Sleep disturbances, appetite disturbances, fatigue, psychomotor agitation or retardation, and changes in concentration, could be counted in a diagnosis of depression only if they were not caused by a physical illness. The exclusive approach simply eliminates fatigue and appetite disturbances from the diagnostic criteria so that the diagnostic process is less influenced by somatic symptoms (Roth et al., 1998). And finally, the substitutive approach is to replace other symptoms of depression when DSM symptoms were problematic. In 1985, Endicott proposed to replace appetite disturbances with fearfulness or depressed appearance. He also proposed to replace sleep disturbances with social withdrawal or decreased talkativeness, and fatigue with brooding, self-pity or pessimism.

Studies that focus on affective/cognitive symptoms of depression identify depressive symptoms better than those focusing on somatic/vegetative symptoms (Jones, Beach, & Forehand, 2001; Hinkin et al., 1992; Kalechstein, Hinkin, van Gorp, Castellon, & Satz, 1998; Penzak, Reddy, & Grimsley, 2000). For example, Jones, Beach and Forehand (2001) conducted an investigation to assess the risks for developing depressive symptoms among 96 HIV-infected African American single mothers. They matched them to a group of 120 demographically similar non-infected single mothers. Self-report and clinician-rated scales of depression were used to assess depressive symptoms at the onset of the study and 12 months later. Regardless of the method of assessment, the findings revealed that HIV-infected mothers had a greater risk to develop depressive symptoms at both assessments. Moreover, HIV-infected mothers remained at greater risk when the

analyses were limited to cognitive and affective symptoms of depression. It decreased the likelihood that the differences were due to greater endorsement of somatic symptoms in the HIV-infected group.

Summary

Fatigue, was a symptom perception that was very difficult to quantify and it has been the focus of a number of descriptive studies. The findings of these investigations shared one commonality: fatigue was highly prevalent and most distressing in people with HIV/AIDS. They become physically and psychologically disabled because of their persistent fatigue experiences. The perception of feeling energy-deprived had tremendous implications, including social isolation, loss of employment, and loss of interest in adhering to HAART. Healthcare providers would need to develop care standards in the assessment and reporting of fatigue. They would also need to screen for the most common causes of fatigue, including anemia, testosterone deficiency (men and women), sleep disturbances and depression.

Conceptual Fatigue Frameworks

A number of conceptual fatigue frameworks have been developed in nursing. Barbara Piper's Integrated Fatigue Model was one of the frameworks applied to fatigue in HIV/AIDS. Nursing models such as the UCSF Symptom Management Model broadened the explanations on symptoms that basic sciences have provided and included additional contexts. Nursing domains, such as (environment, culture, and health), were

integrated. These nursing domains were thought to influence the individual internally and externally, in terms of availability of resources, cultural acceptability or desirability of health practices. The disciplines of medicine and biology reasoned the development of fatigue on a cellular and genetic base. Together, both explanatory strains were important pieces of theoretical information. However, the theoretical frameworks will be presented separately to ensure clarity. First, the biological and medical model will be introduced, then the two nursing frameworks.

HAART and Mitochondrial Intoxication

The discovery of HAART has remarkably decreased morbidity and mortality rates (Rabkin, 2001). The function of HAART would be better understood using some background on the pathophysiology of the HIV virus. The HIV infection is an ongoing process with the production of up to 10 billion viral particles daily (Ho, & Kaplan, 1987). The great number of replications and the imprecise nature of the HIV reverse transcriptase results in as many as 10^4 to 10^5 mutations at each site in the HIV genome each day (Cowley, 2001). Only a full suppression of the HIV replication would hinder the further evolution of the virus. Current treatments suppress the viral replication incompletely. Each antiretroviral agent selects for drug specific mutation sites, known as genotypic resistances. The combinations of antiretroviral drugs are designed to prevent the development of such resistances by suppressing the viral replication as much as possible.

However, the results of numerous studies have shown, that HAART therapy has severe side effects. Nucleoside reverse transcriptase inhibitors (NRTI's), such as

zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T) and abacavir (1592U89) reveal important adverse effects. They range from mild (myopathy) to fatal (pancreatitis, liver failure and lactic acidosis) (Daluge et al., 1997; Adkins, Peters & Faulds, 1997; Lea & Faulds, 1996). Many of those side effects are similar to non-HAART induced mitochondrial dysfunction (see Table 1). All NRTIs listed fatigue as a possible side effect. Increasing evidence has been accumulating that NRTIs cause mitochondrial intoxication and inhibit the replication of the mitochondrial deoxyribonucleic acid (DNA). The basics of mitochondrial function will be provided to better understand mitochondrial intoxication.

Mitochondria are the cell organelles in all body cells except erythrocytes. They contain enzymes and proteins to produce intramitochondrial adenosintriphosphate (ATP), and export ATP into the cytoplasm (Brinkman, ter Hofstede, Burger, Seitlink, & Koopmans, 1998). The most important function of mitochondria is oxidative phosphorylation: the oxidation of fuel molecules by oxygen and the concomitant energy transduction into ATP. Besides ATP production via oxidative phosphorylation, the process of anaerobic glycolysis in the cytoplasm (the conversion of glucose to lactate) generates energy. However, glycolysis produces little ATP compared to the oxidative phosphorylation. In 1998, Brinkman and colleagues found that polymerase γ was needed for the constant replication of mitochondrial DNA (mDNA). If polymerase γ was not produced or suppressed by medication, defects occurred in the mDNA, and lead to an impaired oxidative phosphorylation. As a result, the failure in ATP synthesis could be observed resembling a variety of clinical diseases (see Table 1), and it could affect almost all organ systems. Tissues with the higher energy demand are most susceptible to

Table 1. Clinical Manifestations of Mitochondrial Toxicity

Disorder	Manifestations
Neurological	Peripheral neuropathy, dementia
Myopathy	Muscle weakness, exercise intolerance
Cardiac	Cardiomyopathy
Endocrine	Diabetes mellitus
Gastrointestinal	Pancreatitis, hepatomegaly, liver failure, lactic acidosis
Nephrological	Proximal tubular dysfunction
Hematological	Anemia, thrombocytopenia
Psychiatric	Depression
General	Multiple systemic lipomas, fatigue

Psychoneuroimmunology

The field of psychoneuroimmunology was developed in collaboration with medicine, biology and psychology. It was focused on the interactions of the brain, the immune system, and the physical and emotional reactions of a person. The following description highlights the principals of psychoneuroimmunology. The immune system and the autonomic nervous system are the two major outflow pathways of the brain in its efforts to control the peripheral organs (see Figure 1). The autonomic nervous system innervates the immune system (ex. spleen) through the sympathetic nervous system with catecholamines (nor-epinephrine & epinephrine) to control the organ's functions (Felten & Felten, 1991). The other pathway involves the synthesis and release of releasing factors by cells in the hypothalamus that activate the pituitary gland. The pituitary gland secretes and releases hormones that further stimulate the production of hormones and influence many peripheral immune organs and cells. This interplay is known as the hypothalamic-pituitary-adrenal axis. A variety of stimuli, including "stressors", activate the hypothalamus to release the corticotrophin-releasing hormone (CRH). CRH activates the anterior pituitary to release adrenocorticotropic releasing hormone (ACTH). The ACTH stimulates the adrenal cortex to produce and release blood corticoids (cortisol). Immune organs and immune cells express receptors for these hormones and are being regulated by them (Plaut, 1987).

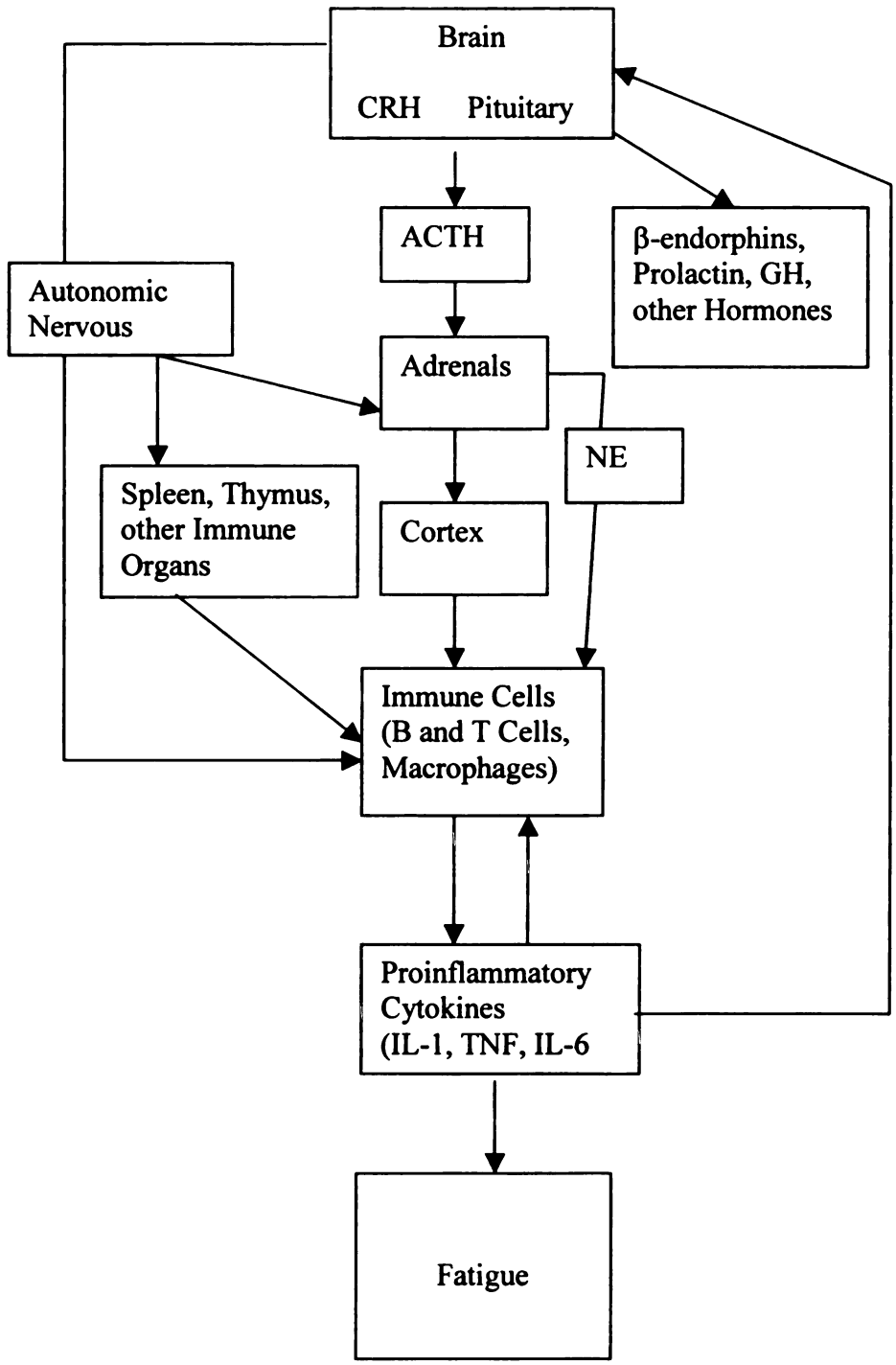
The brain and the immune system form a bi-directional communication network, where products of the immune system communicate with the brain. An infectious or allergic agent can activate the immune system and make it react in a specific or non-specific immune reaction.

In specific immunity, the process starts when a foreign substance (antigen) enters the body. Specific white blood cells, B-cells and T-cells, are activated to fight back the antigen. Memory cells have the ability to detect antigens much more rapidly, using specific receptors, known as immunologic memory. To coordinate and stimulate this complex interplay, all of the immune cells produce cytokines known as interleukins (substances that help them communicate). This process may take about three to five days before the interleukin levels can be detected.

A non-specific immunity is the actual initial defense, which involves a number of different mechanisms. Non-specific immune cells are phagocytes, macrophages and neutrophils. The do not recognize a specific intruder; however, they have the ability to detect a foreign agent in the body and attempt to eliminate it. A large number of immune cells can respond very quickly to an intruder, which makes a more rapid response. After detecting a foreign agent in the body, the macrophages start to produce cytokines called interleukin-1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α). They cause an inflammatory reaction and attract other immune cells that will support wound healing.

Latest research showed that in addition to the local reaction, there is a global reaction to the infection or injury called the acute-phase response (Baumann & Gauldie, 1994) or sickness behavior (Kent, Bluthe, Kelly, & Dantzer, 1992). Physiological adjustments included fever, increased slow-wave sleep, alteration in plasma ions, shifts in the protein production in the liver, and leucocytosis.

Figure 1. Schematic Representation of the Brain-Immune System Connections



In addition there were behavioral changes that included increased responsiveness to pain and reductions in activity, exploration, social interaction, aggression and sexual activity (Kent et al., 1992). Depressed mood was observed (Hart, 1988), as well as cognitive alterations, such as loss of attention and some types of memory deficits (Aubert, Vega, Dantzer, & Goodall, 1995). These behavioral changes function to reduce energy consumption in order to produce fever and to produce energy for physiological functions.

These physiological and behavioral changes acted together as an interrelated system and provided a possible explanation as to why patients with HIV/AIDS experienced fatigue. In the constant fight between the viruses and the CD4+ cells, the immune system elevated cytokine-levels to preserve its energy from behavioral activities. These physiological functions occurred in order to redirect energy towards activities including CD4+ cell production, fever, and reduction of heat loss. As the physical activities decreased, the secondary fatigue would evolve. Physical inactivity would contribute to a diminished physical functioning or disability (Winningham & Barton-Burke, 2000). Furthermore, high levels of depression, anxiety or low self-esteem have devastating psychosocial effects, as well as the accompanied stigma of a positive HIV diagnosis (Robinson, Mathews, & Witek-Janusek, 1999).

In summary, the possible causes of fatigue in HIV were divided into factors, relating to the complex interplay of psychoneuroimmunology. They included hematological changes, activity and sleep changes, hormonal changes, psychological changes, or HAART therapy induced mitochondrial toxicity. They explained why men and women with HIV/AIDS suffered from fatigue. The psychoneuroimmunology model

and the mitochondrial intoxication model had great explanatory power in the physiological development of fatigue. However, according to published studies, there were a number of external factors that influenced the perception of fatigue. These external factors were missing in both models.

Conceptual Nursing Fatigue Theories

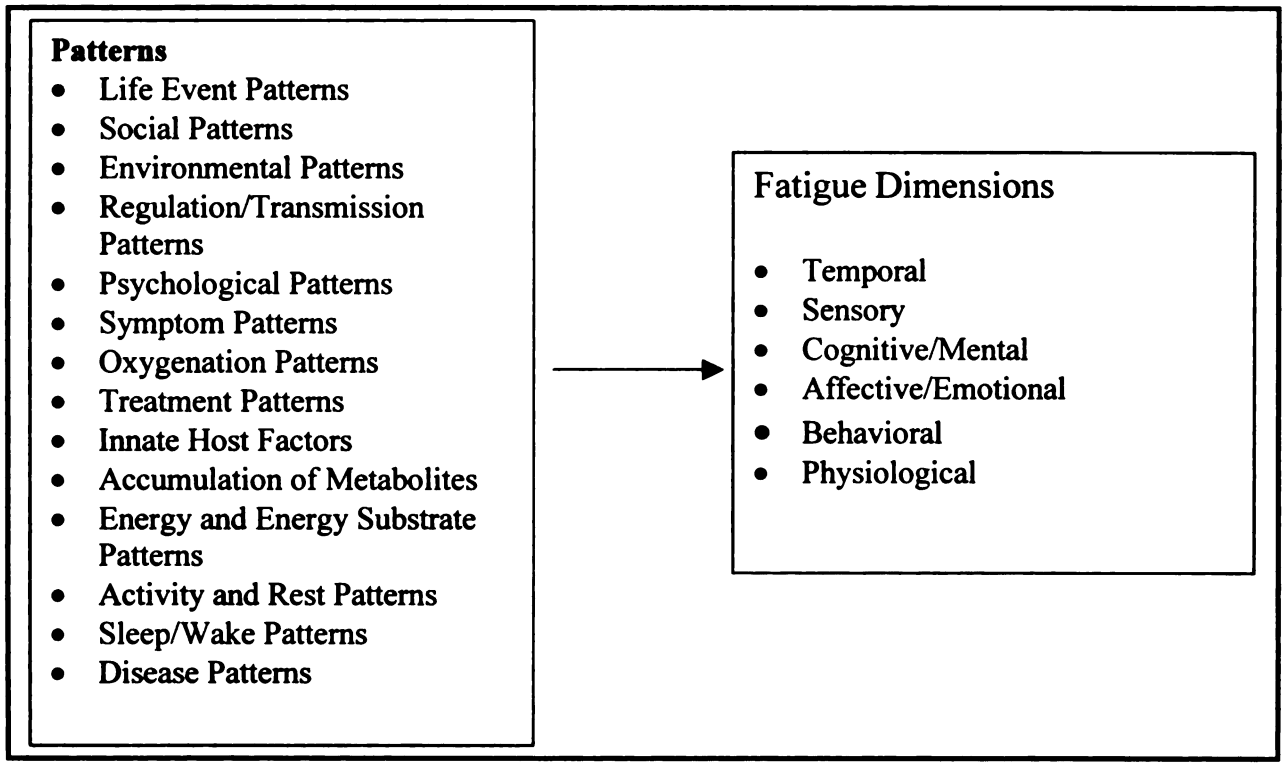
The Integrated Fatigue Model developed by Piper (1998) and the UCSF Symptom Management Model by Dodd and colleagues (2001), offered possibilities to integrate the multitude of expected variables relating to fatigue. In her framework, Piper (1998) integrated the latest findings of medicine and genetics about HIV/AIDS. She contributed to the understanding of the complexity of fatigue in HIV/AIDS patients. Her earlier investigations focused on the division of the fatigue concept into different dimensions. Fatigue was no longer viewed as a single physical dimension, but it was rather divided into physical, temporal, affective and cognitive fatigue dimensions (Piper, 1998). This triggered the development of a series of new fatigue instruments (Piper, 1998; Schwartz, 1999). While fatigue theories were mostly focused on one symptom (fatigue), the field of symptom management frameworks broadened their approach to more than one. Symptom management researchers added additional context to their theory base such as environment or health/illness. Collaborative efforts of nursing researchers at the University of California, San Francisco, School of Nursing, Center for Symptom Management, led to a new area of symptom assessment, management strategies and symptom evaluation. Embedded in the three nursing domains of person, health/illness, and environment was an input-process-output model. Its focus was on the symptom

experience, the management strategies, and the evaluation of the effectiveness. It offered a broader explanation for this multifaceted fatigue concept. Later in the dissertation, both frameworks will be discussed in greater detail, and the current level of application in research and practice will be shown.

The Integrated Fatigue Model (IFM)

In the 1980s, a team of nurse scientists, led by Barbara Piper developed the IFM deductively from the review of literature on fatigue (Piper, 1993; Piper, Lindsey, & Dodd, 1987). It was a comprehensive framework that described 14 biological and psychosocial factors that influenced signs and symptoms of fatigue in clinical populations (see Figure 2). The developers conceptualized a wide range of contributing factors of fatigue to be interrelated. These factors were potentially thought to cause chronic fatigue experiences in both, cancer and HIV patients. In addition, the IFM indirectly gave multiple possibilities on how fatigue was manifested. Also, it provided a base for the assessment of fatigue. The IFM was one of the models proposed to guide HIV/AIDS fatigue research. The model was based on the definition of fatigue in HIV/AIDS, which " is a perception of unusual or abnormal whole-body tiredness disproportionate to or unrelated to activity or exertion. Further, fatigue cannot be resolved with sufficient sleep or rest, and is termed acute when experienced less than a month, and is chronic when the experiences exceed one month " (Piper, 1993, p.213)

Figure 2. The Integrated Fatigue Model



Modified from Piper, B. F. (1998). Fatigue. In: M. E. Ropka, & A. B. Williams. HIV nursing and symptom management Boston, CT: Jones and Bartlett, p. 451.

The theory contained 6 fatigue dimensions: sensory (intensity and local or systemic symptoms of fatigue), cognitive/mental (alteration in memory, concentration, attention, and alertness), affective/emotional (increasing irritability, impatience, lack of motivation, depression), behavioral (impact on activities of daily living), and physiological (changes in laboratory, radiographic, and physical exams). One or more patterns (recurring individual-specific characteristics in a given period of time) could influence each fatigue dimension.

There were 14 types of patterns and 6 fatigue dimensions (see Figure 2). The patterns listed the unidirectional factors that influence the experiences of fatigue in HIV/AIDS (Piper, 1998). The following paragraph will focus on the 14 patterns of theoretically derived relationships, as proposed in Piper's model. The relationship between the accumulation of metabolites and fatigue was supported by findings of the increases of lactate dehydrogenase (ex. Pneumocystis carinii pneumonia and hemolytic anemia in HIV) (Darko et al., 1992). The relationship between energy and energy substrate patterns and fatigue was supported by findings of progressive wasting, weight loss, reduced appetite, malabsorption, and altered malnutrition (Parisien, Gelinas, & Cosette, 1993; Wilson, Roubenoff, Knox, Spiegelman, & Gorbach, 2000). Furthermore, elevated total globulin levels (Darko et al., 1992) and increased resting energy metabolism were also supportive of such a relationship. Decreased motor functioning (Perkins et al., 1995) and decreased functional status (O'Dell, Hubert, Lubeck, & O'Driscoll, 1996) were supportive of activity and rest patterns. Insomnia and increasing total hours of sleep (Darko et al., 1992) supported altered sleep and wake patterns. Findings of lower CD4+ counts and increased fatigue levels (Breitbart et al., 1998; Darko

et al., 1992) supported the relationship to disease patterns. Zidovudine-induced anemia (Fischl, 1989; Fischl et al., 1989) and mitochondrial toxicity (Breitbart et al., 1998; Darko et al., 1992; Freyssenet et al., 1999; Tanaka et al., 1999; Megarbane, Brivet, Guerin, & Baud, 1999) supported the relationship to treatment patterns. The relationship to oxygenation patterns and fatigue was supported by the prevalence of anemia in HIV (Wilson & Cleary, 1996), as well as the complications of HIV-related lung disease (Murray, 1996; Rosen, 1996; Schneider & Rosen, 1997). The relationship of symptom patterns and fatigue was supported by evidence of increased numbers and distress of symptoms, such as pain, diarrhea and night sweats (Lubeck & Fries, 1993; Wilson & Cleary, 1995). Research findings on the relationship between fatigue and psychological patterns were presented (O'Dell, Meighen, & Riggs, 1996; Perkins et al., 1995; Piper, 1993; Wilson & Cleary, 1995). Adrenal insufficiency (Kaplan et al., 1987), elevation of humoral mediators, such as interferon, tumor necrosis factor, interleukins (Piper, 1993) and electrolyte imbalances (Yu-Yahiro, 1994), supported the relationship of fatigue, regulation and transmission patterns. Exposure to noise, heat, allergens and altitude supported the relationship of environmental patterns and fatigue (Piper, 1993). Social, economic, cultural and ethnic differences (Piper, 1993), sexual orientation and drug abuse patterns (Palenicek et al., 1993) supported the relationship of fatigue and social patterns. Significant changes in the lives of people with HIV/AIDS, such as the change or loss of employment or residence, the loss of friends and subsequent grief, supported the relationship of life event patterns and fatigue (Piper, 1993). Finally, Piper stated that differences in innate host factors, such as age, gender (Semple et al., 1993), ethnicity and genetic makeup (Piper, 1993) supported their relationship to fatigue.

Piper contributed significantly to the discourse and the theoretical development of fatigue in HIV/AIDS. However, she had never tested the proposed relationships. The 14 factors were thought to influence fatigue experiences in people with HIV/AIDS. But they were not organized into a system of how much distress they caused, or which of them caused more fatigue. The IFM allowed for the selection of certain factors and the investigation of one or multiple relationships between the factors and the symptom dimensions. Each factor and its relationship along with the fatigue dimensions generated a causal hypothesis.

However, the IFM failed to indicate whether there were relationships in the different patterns, whether there was a reciprocal relationship between the patterns and the dimensions, and if the patterns could be weighted or hierarchically ordered (Winningham et al., 1994). Therefore, the IFM provided limited guidance in managing fatigue and generated 14 unidirectional and testable hypotheses. The IFM also did not provide guidance in the intervention research because the dimension of interventions was not integrated into the IFM.

The Revised Symptom Management Model (UCSF-SSM)

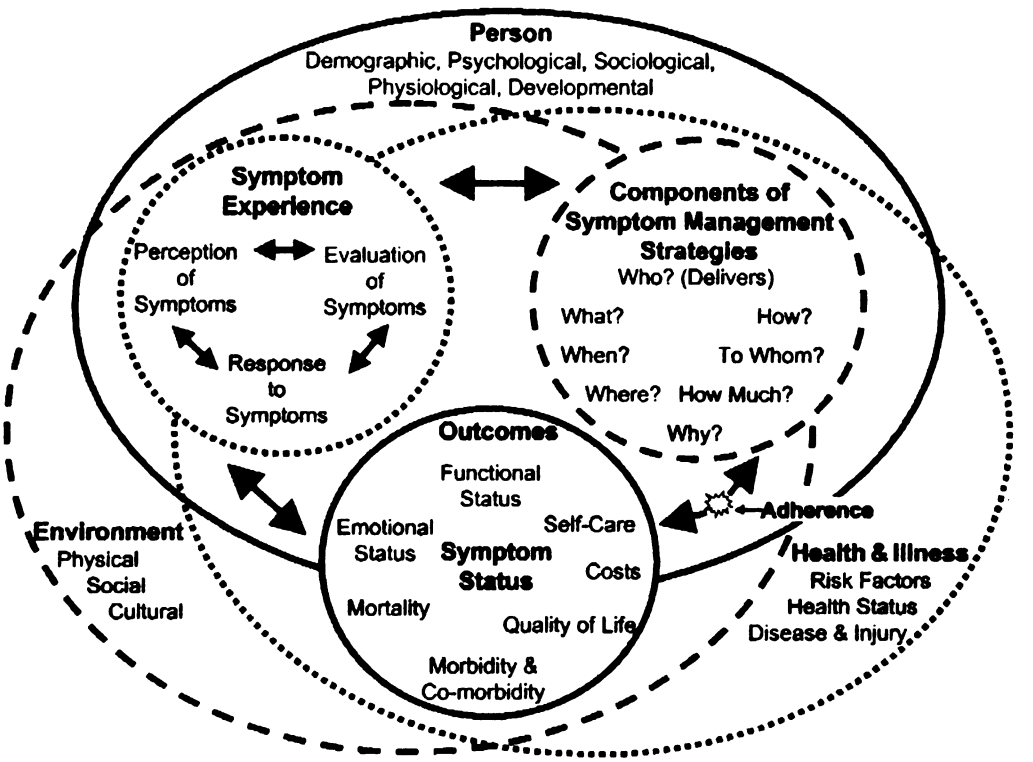
The UCSF-SMM is a multidimensional, (input – process – output model) that is embedded within the three nursing domains: person, environment, and health and illness (Dodd et al. 2001, Larson et al. 1994). It was developed by a number of scholars at the University of California, San Francisco, School of Nursing, Center for Symptom Management and it was the result of an ongoing research. The UCSF-SMM consists of three inner circles that interact within and among each other, one of which is the

symptom experience aka input circle. The second circle is the component of symptom management strategies (process) and the third circle is the symptom status (outcomes). This interdependent process of symptom management is placed within three domains of nursing that interact with each other and the input-process-output components (see Figure 3). The person system represents all the individual variables that influence symptom management and the environment system. The environment system represents all of the social and cultural variables. And finally, the health and illness system represent all the physiological and pathophysiological variables including risk factors, such as injury or infection.

The model is based on six assumptions:

- The gold standard is the patient's self-reporting of symptom experiences.
- The presence of a symptom is not required for the applicability of the model. The risk for developing a symptom is a reason for the initiation of interventions before individual symptoms can be experienced.
- Nonverbal patients experience symptoms.
- Symptoms and symptom interpretation by family members and caregivers is assumed to be accurate information for symptom management.
- Management strategies can be targeted towards the individual, groups, a family, or the work environment.
- Symptom management is a dynamic process, which is modified by individual outcomes and influences.

Figure 3. The Revised UCSF Symptom Management Model



Modified from Dodd, M., Janson, S., Facione, N., Faucett, J., Froehlicher, E. S., Humphreys, J., Lee, K., Miaskowski, C., Puntillo, K., Rankin, S., Taylor, D. (2001). Advancing the science of symptom management. Journal of Advanced Nursing, 33(5), 668-767.

Model Components

Person Domain: The person's views and responses to the symptom experience uniquely define the person variables, such as demographic, physiological, psychological and sociological. Developmental variables encompass the level of maturation of an individual. Depending on the focus, the person variables can be limited or expanded dependent on the symptoms and populations of interest. Lee and Taylor (1996) conducted a study on mid-life women. They documented the impact on the developmental stage of the person and the menopausal symptoms affecting the quality of sleep. Being of female gender affected morbidity and mortality in studies on cardiovascular outcomes with coronary artery bypass graft surgery and after myocardial infarction (Rankin, 1990, 1992).

Health/Illness Domain: Health and illness variables are unique to the states of health and illness of an individual, and include risk factors, injuries or disabilities. Janson and Carrieri (1986) found that different types of pulmonary diseases produced quantitatively and qualitatively different symptom experiences in dyspnea (Janson & Carrieri, 1986). Women who developed non-painful breast abnormalities, as an indicator of breast cancer, were less likely to seek early treatment than those with painful abnormalities, resulting in poorer outcomes (Facione & Dodd, 1998). The type and extent of cancer determined treatment choices and conversely affected risk factors of treatment related morbidities (Dodd et al., 1999).

Environment Domain: Symptoms occur in a specific environment and include physical, social and cultural variables. The home, work or hospital are examples of physical environment, while social networks and interpersonal relationships are the social environment. Cultural aspects of an environment are beliefs, values, and practices defined in part by one's ethnic, racial or religious group. Being temporarily sheltered because of domestic violence had a significant impact on the women's perception of fatigue and sleep (Humphreys, Lee, Neylan, & Marmar, 1999). Asthma patients who were taught in individual self-management sessions had better adherence to therapy and improved medication skills than those taught in groups (Janson, Covington, Fahy, Gold, & Boushey, 1999). An example pertaining to environmental aspects were the results of Lee and colleagues (2000). They found that people with sleep disturbances had different sleep patterns at home compared to a sleep laboratory (Lee, Zaffke, & McEnany, 2000). These three nursing domains of person-environment-health/illness were the basis of the entire model. The central dimensions of the model were the symptom experience, the symptom management strategies and the outcomes.

Symptom Experience: Symptom experience is divided into symptom perception by the individual, evaluation of the meaning of the symptom and reaction or response to the symptom. The perception of pain, for example, depends on one's state of alertness. It also depends on the judgment of every day perceptions and feelings. Pain can be evaluated by judging the severity, cause, treatment options and the effects of symptoms on their lives. Responses to symptoms are multidimensional and include physiological, psychological, cultural and behavioral components.

Symptom Management Strategies: Symptom management are necessary to prevent or manage negative health outcomes through professional and self-care strategies. Identifying the focus for interventions follow symptom assessment. Interventions target one or multiple symptoms and try to achieve the desired outcome. This process is dynamic and requires frequent changes in strategies. These strategies were defined by what, when, where, why, how much, to whom and how these interventions would be delivered.

Symptom Outcomes: Desired outcomes might emerge simultaneously from symptom management strategies and from the symptom experience. Outcomes can be influenced by eight factors such as functional status, emotional status, mortality, morbidity/comorbidity, quality of life, costs, self-care and, central to all of them, symptom status. These factors indicate no directional relationship between the factors and the symptom status. They are understood as related to each other, as well as to the symptom status. The UCSF-SMM is a relevant model for the treatment and prevention of symptoms, and it is relevant for as long as the symptoms are perceived, the need for interventions persists, or the treatment does not resolve the issue.

The application of the current knowledge on fatigue in HIV into the UCSF-SMM offered systematic understanding of current research findings and also offered directions for further research. In the person domain, individual variables influenced the levels of fatigue in a person with HIV/AIDS and included: age, gender, ethnicity, income, educational background, coping styles, etc. This domain also integrated the complex interplay of psychoneuroimmunology and HIV. The health and illness domain contained

the HIV disease itself, co-morbidities, in addition to the risk factors such as addiction or multiple stressors. In the environment domain, the employment, residence, and hospital influences were encompassed. In addition, the impact of social networks and culture-specific beliefs, values and practices on fatigue were to be included in this domain. The symptom experience dimension included the measurement issues of fatigue in HIV, as well as the other symptoms that accompanied the disease. Also, Piper's fatigue dimensions were represented within the symptom experience dimension. The symptom management dimension encompassed the interventions including testosterone supplementation, physical exercise, and psychostimulants. The outcome dimension included the concepts that provided opportunities to evaluate the effectiveness of the interventions.

The UCSF-SMM has been the most elaborate model for symptom management, applicable not only to fatigue in HIV/AIDS but also to all symptoms of all people. It was the guiding framework in this research on fatigue in HIV. The UCSF-SMM is still an evolving model and some issues need to be investigated further. For example, more studies should be conducted on simultaneously occurring symptoms or symptom clusters. The model focused on primary symptoms in the forefront (including fatigue). However, rapid changes within a symptom cluster could shift the symptom from the forefront and into the background. This would mean that another symptom, such as neuropathy became more or less severe or distressing. Symptom clusters were symptoms that occurred together. They influenced each others' intensity, duration and distress (Newshan, Bennett & Holman, 2002). These changing patterns were currently not represented in this model.

Both theories provided a multifaceted possibility in explaining the complex interrelationships between fatigue and HIV/AIDS. For this study, the UCSF-SMM nursing framework was chosen to be the guiding theory in the approach of the secondary data analysis, including the hypothesis development, the reporting of the results and well as the discussion.

Measures of Fatigue

Fatigue measures have been developed over the last 90 years by different scientific disciplines, such as ergonomics, economy, medicine, and psychology. These different disciplines have influenced the development of fatigue measures in nursing. This section is divided into five parts: fatigue-specific measures, symptom checklists, depression measures, quality of life measures, and physiological measures. In each part, the most frequently used instruments in HIV/AIDS research were analyzed and issues of reliability, validity, and utility were addressed. The summary will include a brief synopsis of the measurement issues regarding fatigue in HIV/AIDS and a discussion about existing gaps within these instruments.

Fatigue-specific Measures

Measuring fatigue dates back to the First World War (1914-1919), when ergonomic scientists assessed fatigue in workers of the munitions industry. Investigators focused on the impact of fatigue on the efficiency and productivity of the industrial workers (Ream, & Richardson, 1999). In the 1950's, fatigue research continued in airmen from the Second World War (1939-1945) (Pearson, & Byars, 1956). They utilized a symptom checklist, which focused on subjective fatigue in relationship to the psychomotor tasks of pilots. Later, nurses started to use these symptom checklists in several studies (Haylock, & Hart, 1979; Rieger, 1988). Most of the earlier measurement tools, such as Yoshitake's Fatigue Scale (1971) and Pearson and Byar's Fatigue Feeling Tone Checklist (1956, 1957) were developed for the assessment of healthy subjects. At the time both instruments were rigorously developed. However, they were no longer used,

because the language was outdated and less clinical applicable. Fatigue measures in the 1980's and 1990's became of interest to nurses and physicians because of the developments in the treatment of cancer, as well as other chronic illnesses.

The development of fatigue measures advanced further with the creation of Piper's Fatigue Scale (PFS) (Piper et al., 1989) and Lee's Visual Analog Scale-Fatigue (VAS-F) (Lee, Hicks, & Nino-Murcia, 1991) (see Appendix 2). Piper and colleagues (1989) originally created a fatigue-specific instrument with 71 items. It assessed the presence of fatigue, distress, emotional impact, behavioral impact and social impact. However, the instrument was not utilized because of its length. Subsequently, the PFS was revised twice. The latest version of the PFS (1998) has 22 items that can be scored

into a total fatigue score, and four subscales measuring behavioral/severity (6 items), affective meaning (5 items), sensory (5 items) and cognitive/mood (6 items) (Piper et al., 1998). The revised PFS reported excellent reliability and validity data (see Appendix 2).

In a small study with 6 gay men with HIV/AIDS (Voss, 2001), the PFS proved to be highly acceptable. The subjects were asked to complete the questionnaire and give their opinions on the instrument. These qualitative responses on the PFS were indicative that the instrument was easy to complete, and appropriate in length. Minor modification suggestions were made. One of the modifications was in the first question that asks about the time their fatigue persists. The answer choices were minutes, hours, days, weeks and months. Four of the six respondents suggested that years should be added as a choice. Of the six respondents, four reported ongoing fatigue and identified the time they were infected with HIV as the time they started to perceive a sense of fatigue. None of these men experienced the previous level of energy they had before their infection.

Lee and colleagues (1991) developed an 18-item Visual Analog Scale-Fatigue (VAS-F). It contains five items that measure energy and 13 items that measure fatigue. The original scale had word anchors and the participants were asked to rate the items on a visual analog scale (VAS) from 0-100. Later this was revised to 0-10 point numeric rating scale, with comparable reliability coefficients (Lee, Portillo, Miramontes, 1999). The use of VAS-F has had strengths and weaknesses. The VAS-F was convenient, easy to administer and useful in a variety of clinical and research settings (Lee, 1991). However, investigators (Huskisson, 1983; Williams & Rabkin, 1991) reported difficulties in completing visual analog scales in general. Some subjects did not understand the word anchors or did not understand how to complete the VAS. In the past, a concern with any

VAS was the quality of photocopying, which resulted sometimes in different lengths of the lines. Aaronson and colleagues (1999) reported that numeric rating scales were less influenced by eye-hand coordination problems. They were easier to score for computer analysis, and they yielded similar data to visual analog scales (Aaronson et al., 1999).

Circadian rhythms and hormone levels have been shown to have a direct relationship to fatigue and the physical and emotional perception of a person (Atkinson, & Reilly, 1996; Moldofsky, 1995). Circadian rhythm differences (morning/evening) as a response choice was missing on most fatigue instruments. Only the Visual Analog Scale Fatigue (VAS-F) by Lee and colleagues (1999) had been used to assess the aspect of fatigue differences in the mornings and in the evenings. The importance of circadian differences in symptom reporting was much better understood, when a study participant mentioned that his perceptions of fatigue were completely different at different times of day (Voss, 2001). The results of his instrument ratings would vary greatly according to time of the day the questionnaire was completed.

To date, the diversity of different fatigue measurement has been in its developing stage. Lee's instrument (1991) had the advantage of integrating circadian rhythms and measures of fatigue and energy. Piper's instrument (1998) had the advantage of being multidimensional. However, Barroso and Lynn (2002) compared and contrasted a number of fatigue scales and discovered that the findings of the qualitative study they conducted, were not reflected in the answer choices of the current fatigue instruments. They classified the dimensions of fatigue and divided them into three categories: intensity, circumstances surrounding fatigue and consequences of fatigue. As a result of their study, they developed a new 53-item HIV-Related Fatigue Scale (HRFS), most of

which used a 0-10 numeric rating scale and were drawn from five existing scales. Cronbach's alpha was 0.94 for the entire tool, which might indicate repetitiveness of the items. Test-retest validity was moderate at a 2-day interval (r = 0.4).

Symptom-Checklist

Symptoms have been the identifying pattern of most diseases. Therefore, symptom checklists helped screen and rate the presence and absence of different symptom profiles. Symptom checklists were available for a variety of diseases and were disease specific. Because fatigue was a common symptom in many diseases, it was found in several symptom instruments. Several symptom checklists for cancer and HIV/AIDS had certain commonalties, such as the Adapted Symptom Distress Scale-2 (ASDS-2) (Rhodes, McDaniel, Homan, Johnson, & Madsen, 2000), the Revised Sign and Symptom Checklist-HIV (SSC-HIVrev) (Holzemer et al., 1999; Holzemer et al., 2001) and the Memorial Symptom Assessment Scale- Short Form (MSAS-SF) (Chang, Hwang, Feuerman, & Kasims, 2000) (see Appendix 3). Usually these instruments listed a number of symptoms or symptom-clusters. They asked patients to check the ones they have experienced in the last week or that day. On either 3 or 7-point Likert scales, the symptoms could be rated for their presence and their intensity. Symptoms could have occurred through the disease, but also as side effects of treatments. Checklists often included signs and symptoms that became present through disease-specific treatments (mouth sores, numbness/tingling in hands and feet, lipodystrophy, etc.). Fatigue was an important symptom to screen and was included in all of the reviewed measures. Appendix 3 provides information on the reliability, validity and utility of the different

symptom checklists. The reviewed symptom checklists reported excellent reliability and have been validated in many investigations. The major differences in the checklists were the number and type of symptoms that could have been checked. Checklists for cancer patients tended to be shorter than checklists for HIV/AIDS patients. While men and women with HIV/AIDS have participated in using the checklists, only one of the checklists included eight specific gynecological symptoms, the SSC-HIVrev (Holzemer et al., 1999; Holzemer et al., 2001).

As an example of construct validity, the MSAS-SF predicted life expectancy (Chang et al., 1998) in cancer patients. Chang and colleagues (1998) found that lower MSAS-SF physical symptom score significantly predicted survival and added to the prognostic information of the KPS score ($P< 0.001$). They further stated that patients tend to be under-assessed for both the number and the severity of symptoms. Holzemer and colleagues (1994) validated the hypotheses that healthcare providers consistently underestimated the number and the distress of symptom experiences in their patients. For fatigue, the agreement ratings between nurses and patients reached only 53%, which meant that nurse's identification of their patients' fatigue as a problem was just by chance. Holzemer (2001) wrote that the patient had to be considered the gold standard in the assessment of their symptom experiences. Patients experienced symptoms in a unique way (Reilly, Holzemer, Henry, Slaughter, & Portillo, 1997). Therefore, they needed to be asked about the distressing symptom experiences. Fatigue, for example, tended to be neglected frequently because of the inability of patients to explain the burden of it.

The revised SSC-HIVrev was currently the most encompassing instrument to assess signs and symptoms of HIV/AIDS. The instrument covered 64 physical signs and symptoms, 4 psychological symptoms and included 8 women-specific symptoms. The SSC-HIVrev reported excellent psychometric properties and demonstrated to be a good instrument for English-speaking adult HIV/AIDS patients. It has been translated into Spanish, Norwegian and Chinese, and it has been successfully tested in these countries or within these cultures. However, further testing would be necessary in culturally diverse samples to prove if the word choices for symptoms would be culturally sensitive. In a sample of African-Americans, several participants had questions about the meaning of the selected words that described symptoms. In addition, the SSC-HIVrev focused on the presence, absence and frequency of 74 symptoms, including fatigue. To capture in-depth all dimensions of fatigue, a more fatigue-focused instrument would be necessary.

Depression Measures

Generally, depression scales were divided into provider rating scales such as the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), or the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery, & Åsberg, 1979), and self-rating scale such as the Beck Depression Inventory (BDI) (Beck, Ward, & Mendelson, 1961) or the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). Clinician rating scales, such as the HRSD or the MADRS were developed to assess the severity of depression in patients that have already been diagnosed with clinical depression. Unlike most of the depression scales, the MADRS did not include fatigue. The HRSD was one of the most widely used depression instruments and it was

utilized in at least 500 published studies over the past ten years (Hooijer et al., 1991). It required trained raters to complete the questionnaire through an evaluative interview. Fatigue was included in the physical symptom questions, but altogether, the physical symptoms contributed only 8 points to the total score of 64. The potential of misdiagnosing a severely fatigued person as depressed was rather small because there were only 8 of 64 items.

Typically, fatigue items were included in depression measures. Fatigue was one major symptom of depression. Other physical symptoms of depression included: sleep disturbance, lack of appetite and unintentional weight loss or gain. Depression was detected and diagnosed by a number of widely different symptoms. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the 17 diagnostic criteria for depression included a minimum of five physiological and psychological symptoms. They had to occur during a two-week period and had to cause a change from prior functioning (American Psychiatry Association, 1994). Physiologic characteristics for depression were unintentional weight gain or loss, daily insomnia or hypersomnia, and fatigue or loss of energy. Psychological characteristics for depression were loss of interest, depressive mood, psychomotor slowing, lack of concentration, suicidal thoughts and feelings of guilt and unworthiness (APA, 1994). For a definite diagnosis of depression certain symptoms have to be present, including depressive mood, loss of pleasure or interest in life. Aside from feelings of worthlessness and suicidal thoughts, all other characteristics fit the description of patients with severe fatigue (Hintz, Kuck, Peterhin, 1990; Ostrow, Grant, & Atkinson, 1988). This overlap made the differentiation between depression and fatigue, and the measurement of these concepts, quite difficult.

Diagnostic measures of depression required the exclusion of possible explanations, including physiological effects of medication or medical conditions, such as hypothyroidism or schizophrenia. In addition, clinical ratings have recorded nonverbal indicators of depression. Also, they could handle distorting factors, such as denial and exaggeration.

Self-rating scales were widely accepted as self-assessment tools to identify the syndrome of depression. They were less expensive and were found more frequently in clinical research, and they emphasized subjective and affective elements of depression. The disadvantage of self-rating measures was a lack of specificity: for example, the BDI did not distinguish between depression and fatigue. This resulted from the emphasis on physical symptoms in the instrument. The BDI uses total score ranges as cut-off points for depression. For the BDI, the total scores range from 0-63, where fewer than 10 points indicate no depression, 11to 18 points indicate mild to moderate depression, 19 to 29 points indicate moderate to severe depression, and finally scores greater than 30 indicate severe depression. The BDI covers 21 symptoms, of which 11 cover emotions, four cover behavioral changes, and six cover physical symptoms. If, for example, a person with severe fatigue scores the highest possible score of all six physical symptoms, this person is considered to be moderately to severely depressed. If the same person has trouble concentrating, looses interest in the outside world or has a total score beyond 30, the BDI categorizes them, severely depressed. But in fact he or she might not be depressed at all; he or she might be severely fatigued. The somatic symptoms of depression sometimes lack accuracy by self-assessment and often produce false-positive results in ill and elderly

people (Beck, Steer & Garbin, 1988). Furthermore, depending on the level of depression, patients might have over-or-underestimated their levels of depression.

Another self-rated screening tool for depression is the 20-item CES-D instrument. The scores range from 0-60 where a score higher than 15 indicate possible clinical depression. The emphasis of the CES-D is on affective components: depressed mood (6 items), feelings of guilt and worthlessness (6 items), feelings of helplessness and hopelessness (3 items), psychomotor retardation (3 items), loss of appetite (1 item) and restless sleep (1 item). Only two physical symptoms – restless sleep and loss of appetite contribute to the total score, which give physical disturbances less emphasis.

In early descriptive reports of psychiatric disorders in people with HIV/AIDS, most self-report rating scales yielded extremely high levels of symptomatic depression and anxiety (Bellini et al., 1994; Hinkin et al., 1992; Lyketsos, Hanson, Fishman, McHugh, & Treisman, 1994). After a closer investigation of this phenomenon, Rabkin (2001), attributed many of the findings to a mismanagement of symptoms, including fatigue and sleep disturbances. Joseph and colleagues (1990) conducted a cohort study with bi-annual evaluations for depressive symptoms. The study followed 436 subjects over a three-year period, using the CES-D5 (an abbreviated version of the CES-D). Their results indicated that depressive symptom scores remained stable over the period of the three years. This meant, the incidence of depression did not increase or decrease with the progression from HIV to AIDS (Joseph et al., 1990).

The BDI and the CES-D are widely used instruments with HIV/AIDS patients. Both are designed to be self-administered. The Beck's Depression Scale was specifically developed for psychiatric patients, and the CES-D had a more general population focus

(see Appendix 4). Generally, both instruments demonstrated reliable and valid findings in numerous studies with multiple groups of patients. The BDI was specifically measuring the depth of depression, whereas the CES-D was a general screening tool for symptom frequency. However, both tools have limitations. The BDI was criticized for the limited scope of the scale; and furthermore, for the somatic content which led to false-positive results in physically ill patients (Beck et al., 1988). It was also suspected to have a social desirability response bias (Cappeliez, 1989). The CES-D had limitations too, and should not have been used as a diagnostic tool. It could not distinguish between a primary and a secondary diagnosis of depression. This would have required different types of treatments (Weissman et al., 1977). Further, it fails to separate general depression from anxiety and fails to distinguish past from present disorders (Rabkin & Klein, 1987).

Depression in HIV/AIDS patients is a serious problem and affects about 4 to 14% of gay men and non-drug using women, with higher rates among infected and non-infected drug users (Rabkin, 2001). Judith Rabkin presented evidence that there was no direct link between HIV disease and depression. She wrote that: " The majority of HIV-infected people with current depressive disorder have a history of depression that precedes HIV infection, and depression is not correlated with disease stage, T-helper cell count, or HIV-related medication use"(p.1).

A study conducted at Cornell University, followed 328 seropositive and seronegative gay and heterosexual men and women for a period of 1 year. The goal was to assess the severity of their depressive symptoms (Perry, Fishman, Frances, & Jacobsberg, 1992). They found a decline in the severity of depressive symptoms with

both clinician and self-report scales. Over time, there were no significant differences between infected and uninfected subjects.

Multiple investigators conducted clinical trials to assess different types of treatments for depression and found significant improvements (Breitbart et al., 2001; Griffin, Rabkin, Remien, & Williams, 1998; Wagner, Rabkin, & Rabkin, 1997; Wagner & Rabkin, 2000). Breitbart and colleagues (2001) conducted a six week randomized drug trial to investigate whether two types of psycho-stimulants were equally effective in reducing fatigue. They found significant decreases in the Piper Fatigue Scale (PFS) total score for patients receiving methylphenidate or pemoline compared with subjects receiving placebo ($F_{2,116} = 4.63$, $p = .02$). In addition, the depression scores of patients decreased as well, meaning that there could have been significant interactions between the two symptoms. In this sample, the effects were due to a general decrease of depressive symptoms, rather than a decrease in fatigue. They argued that the improvements in depressive symptoms were less correlated with the affective subscale of the PFS, and much more correlated with overall fatigue improvement and fatigue severity. This suggested that the antidepressant effects were mainly due to a decrease in the severity of fatigue, rather than the direct antidepressant effect of these medications. The challenge in the future would be to further distinguish clinical depression from fatigue.

Quality of Life Measures

Quality of Life (QOL) measures have received great attention because of the successes of prolonging life and the subsequent challenges people faced with their extended lives. Seriously ill patients have expectations about their quality of life and survival alone is not a sufficient quality of life indicator. QOL has no universal definition, but the literature agrees on a number of concepts under the umbrella of health-related quality of life. QOL instruments measure diverse aspects of health and are generally intended for outcome research (see Appendix 5).

Dimensions of health-related QOL included physiological symptoms, functional status, social functioning, role functioning, and psychological well-being (Cleary et al., 1993; Copfer et al., 1996). The symptom experiences in people with HIV/ AIDS made measuring energy and fatigue an important issue in the QOL literature (Spitzer et al., 1981). In 1981, Spitzer and colleagues developed the Quality of Life Index (QOL-I) for people with AIDS. The instrument measures five dimensions of quality of life: activity, daily living, health, support and outlook, and it uses a 3-point Likert scale, which can be summarized into a single total score for QOL. The QOL-I exists in two versions: a self-administered and a provider-administered version. The instrument was widely used as a quick assessment tool for seriously ill people. However, serious limitations with sensitivity to short term changes were reported (Levine et al., 1988; Williams & Rabkin, 1991). Two studies reported difficulties in detecting differences between groups. Williams and Rabkin (1991) examined the content validity of the QOL-I in a sample of HIV-positive and HIV-negative males and could not find any differences. Similarly, Levine and colleagues (1988) examined the QOL-I in two samples of women with breast

cancer and used both types of the QOL-I, using self-rating and nurse rating as methods for data collection. Over a two-week period, the women had not changed in physical or emotional functioning, as rated by their study nurse; however, the QOL-I self-rating scale scores showed a significant decline. Levine and colleagues suggested the nurse's ratings missed the deterioration of the patient or that there was a measurement error in the scales (Levine et al., 1988).

Two explanations might explain the findings of Williams and Rabkin (1991) and Levine and colleagues (1988). First, there might be little agreement on the perception of nurse and patient's ratings (Henry et al. 1994; Holzemer, et al. 2001). Levine and colleagues did not acknowledge change in the patients' ratings because they assumed that the ratings between patients and providers were identical, and therefore discarded the patient findings. Such assumption had been proven to be inaccurate in more than one study (Henry et al., 1994; Holzemer et al., 1999; Justice, Rabeneck, Hays, Wu, & Bozzette, 1999). Second, being HIV-positive did not automatically imply that the quality of life was diminished. The life of an asymptomatic gay man infected with HIV might not be that different from a healthy one. Spitzer and colleagues' (1991) findings suggested that the QOL-I was not suitable for healthy respondents, instead survey measures, such as the Medical Outcomes Study Short Form-36 (MOS SF-36), might be more appropriate.

One of the early measures for quality of life is the 20-item Medical Outcomes Study Short Form-20 instrument (MOS SF-20), derived from the work of the RAND Corporation, in Santa Monica, California. The RAND Health Insurance Experiment compared the impact of alternative health insurance systems on health status and utilization. The MOS SF-20 had been used extensively and partially incorporated into

many different instruments (Lohr et al., 1986). The MOS SF-20 (Stewart, Hays, & Ware, 1988). It had been used multiple times to measure health-related quality of life in HIV/AIDS (Holmes, Bix, Meritz, Turner, & Hutelmyer, 1997; Smith, Avis, & Assmann, 1999; Smith, Avis, Mayer, & Swislow, 1997; Smith et al., 1996; Wu, Hays, Kelly, Malitz, & Bozzette, 1997). Stewart and colleagues (1988) developed an instrument to measure general health status with six dimensions: physical, role, social functioning, mental health, health perceptions and pain. Higher total scores in the six dimensions indicate higher functioning and lower symptom distress, which means a higher quality of life. Questions about fatigue were not included in this version of the MOS SF-20.

Fatigue was one of the primary symptoms experienced by people with HIV/AIDS (Boyko et al., 1987; Harms, Laukamm-Josten, Bienzle, & Guggenmoos-Holzmann, 1987; Kaplan et al., 1987). Wu and colleagues (1991) decided to integrate a subscale on fatigue into an adapted version of the Medical Outcomes Study-HIV (MOS SF-HIV) instrument. They took 16 original items from the MOS SF-20, developed 14 new items, and increased the number of scales from six to ten and the number of items from 20 to 30 (Wu et al., 1991). However, they kept the MOS SF-HIV brief enough to be completed by seriously ill or disabled patients. In addition, the MOS SF-HIV included a scale on cognitive functioning to assess the increasing numbers of cognitive problems of HIV/AIDS patients. Appendix 5 lists reliability, validity and utility data for the QOL-I, the MOS SF-20, the MOS-HIV and the MOS SF-36.

Each of these instruments has limitations. For example, investigators reported significant floor and ceiling effects on the MOS-SF-20 and the MOS SF-36. The role functioning scale in the MOS SF-20 was previously reported as an item with a high rate

(8%) of missing data (Bindman, Keane, & Luire, 1990). Wu et al. (1991) reformatted the items on the role functioning scale as recommended by Stewart, Hays, and Ware. Nevertheless, the problem with high rates of missing data persisted. This might be attributable to the wording of the MOS SF-36. Because of the tremendous societal pressure and marginal position of people with AIDS (PWA), many infected gay men continued enormous efforts to be involved in the gay community and in HIV/AIDS support groups. Despite the devastating effects of opportunistic infections, these gay men increased, rather than decreased, their role functions and retained their roles as board members, group leaders, volunteers or organizational members. The response options regarding role function were not answered because the choices might not have been applicable to respondents. All of the response choices were worded towards unchanged or limited role function, with none phrased to address increasing role function.

Because the MOS SF-20 lacked critical concepts, such as vitality and role limitations due to physical and emotional problems (Bindman et al, 1990), the RAND-Corporation decided to develop the Medical Outcomes Study Shortform-36 (MOS SF-36). The MOS SF-36 has eight dimensions: physical functioning, role limitations due to physical health problems, bodily pain, role problems due to personal/emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions to measure general health status. The MOS SF-36 has become one of the most widely distributed and validated instruments among the QOL-measures (McDonnell, Gielen, Wu, O'Campo, & Faden, 2000). Translations are available in 30 different languages, and the MOS SF-36 has been used in many different populations (multiple age groups) (McHorney, Ware, Lu, & Sherbourne, 1994), across different diseases (dialysis patients,

patients after a knee-replacement, and other diagnosis groups) (Kantz, Harris, Levitsky, Ware, & Davies, 1992; Kurtin, Davies, Meyer, De Giacomo, & Kantz, 1992; McHorney et al., 1994) and proved to be an excellent health status measure (Aaronson et al., 1992; McHorney et al., 1994; Wagner, Gandek, Aaronson et al., 1998). However, the MOS SF-36 showed ceiling effects for the results in geriatric groups on the physical functioning dimension (McHorney et al., 1994). Ceiling effects have been observed when the values of most subjects fell on the upper end of a scale or an instrument; Nunnally and Bernstein referred to ceiling effects as the "perfect score" (Nunnally, & Bernstein, 1994) p. 570.

For the applicability in some European countries, the MOS SF-36 needed to be adjusted in its word choices to be meaningful ('having the blues' was changed into 'feeling down'). Physical functioning was one of the biggest challenges to be translated into 10 different cultures. While bowling and playing golf, listed as examples for moderate activities, were quite common activities in the United States, they were rather uncommon activities in the majority of European countries. Playing golf was translated into riding a bicycle in Italy and the Netherlands, walking in the forest or gardening in Sweden, and walking more than one hour in Spain (Wagner et al., 1998). Comparing the results of the reliability coefficients among 11 different countries, no significant differences were found among the countries. The range of coefficients for the eight scales ranged between 0.76 and 0.92 for Denmark, between 0.79 and 0.91 for France, between 0.74 to 0.93 for Germany, between 0.84 and 0.93 for the United Kingdom, and between 0.68 and 0.93 for the United States. The items discriminated well across scales for most items in all countries. For example, the role-physical and the bodily pain scale had a 100% scaling success rate across all countries. Differences were found in the vitality and

the mental health scale in several countries. The vitality item "full of pep" had a higher correlation with the mental health scale than the vitality scale in Italy and the Netherlands. This was considered a definite scaling failure. However, items generally correlated significantly higher with their own scales than with competing scales, supporting item discriminant validity. Scales could be constructed for 93-100% of the respondents.

Physiologic Measures

Physiological measures or biomarkers related to fatigue often do not contain clear-cut information or are entirely dependent on the clinical focus of the investigators (HIV/AIDS, nutrition, endocrinology, neurology, etc.). There are multiple methods and issues around biomarkers, such as immunological markers, red blood profiles, cytokines, hormonal levels, muscle-mass, fat-free-mass and lactic acid levels. This section focuses on several types of blood profiles such as CD4+ count, viral load, hemoglobin, hematocrit, cytokines and hormonal levels.

HIV/AIDS experts assess the HIV status of their patients' immune function with a number of immunologic parameters, such as CD4+ count, viral load, p24 antigen, and viral resistance testing. In relation to fatigue, only CD4+ cell counts and viral load have been tested for significant relationships. Increasing evidence show that fatigue and CD4+ cell counts are not related. While studies in the early 1990s found significant relationships between fatigue and CD4+ cell counts, in the findings by Breitbart and colleagues (1998), they did not show a relationship between the number of CD4+ cells and fatigue. The mean CD4 count for patients with fatigue was 191 ± 167, the mean CD4

count for patients without fatigue was 202 ± 260), which was statistically insignificant. Cunningham and colleagues (1998), Perkins and colleagues (1995), Lee and colleagues (1999) and Singh and colleagues (1997) also found insignificant relationships between fatigue and CD4+ cell counts. It was unclear if the number of CD4+ cells was directly related to the experience of fatigue. One factor that contributed to these conflicting results was the method of data collection. Namely, these included whether the CD4+ counts were collected from direct blood specimen collection and immediate testing, or abstracted from medical records, which may be incomplete or outdated, or through self-report which had been documented to be unreliable. But even direct blood specimen collection could have resulted in dramatically fluctuating results. CD4+ cell circadian rhythm results in fluctuations of as much as a 150-300-cell/mm^3 difference between morning and evening values in a normal host (Malone et al., 1990). Additionally, the longer it takes to process the blood samples, the more likely CD4+ counts are artificially elevated. Refrigeration can also dramatically increase CD4+ counts. Increasing scientific evidence supports the conclusion that CD4+ count levels are not predictive of fatigue.

Viral load measurements are standard in clinical practice (Saag et al., 1996, Haddad et al., 2000). Quantitative polymerase chain reaction (PCR) and branched-chain DNA (bDNA) demonstrate independent predictive value in determining the relative risk of clinical progression and/or survival when compared to other markers (Saag et al., 1996). The greatest strength of the PCR is also its greatest weakness – its incredible sensitivity. When the procedure is performed properly, there is no better molecular biological technique. However, even in highly specialized laboratories, inadvertent contamination of reagents or target DNA or both led to false-positive results (Lifson et

al., 1990). A novel non-PCR-based technique called bDNA technique is an Enzyme Linked Immunosorbent Assay (ELISA-like assay). It amplifies signals from target HIV RNA or DNA using a series of branched probes. It has advantages over other methods because it is easy to use and can analyze other subtypes of HIV-1, commonly found outside the United States (Cao, Ho, & Todd, 1995). A limited number of studies tried to correlate HIV viral load and fatigue, and found no significant relationship between them (Badia et al., 1999; Ferrando et al., 1998; Borman, Shively, Smith, & Gifford, 2001).

Erythrocyte blood count, hemoglobin, and hematocrit, as measures for anemia, provided important information on the energy level of patients. Anemia in HIV disease is well known to cause severe fatigue through the lack of oxygen in every human cell (Semba & Gray, 2001). Cosby and colleagues (2000) found, in a sample of HIV-infected men and women, that there was a significant relationship between treatable hematocrit (indicator for anemia) and CD4+ counts ($p = 0.013$), but that there was no significant relationship between hematocrit and fatigue (Cosby, Holzemer, Bakken Henry, & Portillo, 2000), possibly because all interviews were conducted on the first or second day after patients were admitted into the hospital. Clinically, it might have taken 24 hours to a number of days to recognize the subjective effects of transfusions or the treatment with erythropoetin for anemia and other types of cytopenia (Biesma, 1999; Coyle, 1997). The physiologic changes were easier and more reliable to assess than the patients' perceptions. If the hemoglobin was below 8.0, and the anemia was only short-term, effects of blood transfusions could have been directly observed. Patients could have expressed having more energy after receiving blood, they could have been able to breathe easier, and they could have expressed a general sense of well-being. If anemia persisted

over a long period of time, the difference for patients pre and post treatment were insignificant, because they had adapted to a lower level of oxygen (Biesma, 1999; Coyle, 1997).

In general, laboratory values, retrieved from blood samples, are more specific and sensitive than patients' own self-recall of the values. Fowels, Rosheim, Fowler, Craft, and Arrichiello, (1999), conducted a study with 440 diabetes patients to validate self-report in comparison to record data on hemoglobin A_{1C}. They calculated the sensitivity and specificity, positive predictive value and negative predictive value for the two values. For hemoglobin A_{1C}, 239 subjects reported values compared to their medical records that were 98.8% sensitive to detect pathological values; while 28.3% of the values correctly defined the patients who did not have pathological values, 84.8% of hemoglobin levels predicted diabetes and 85% predicted the absence of the disease (Fowels et al., 1999). Self-report of hemoglobin tests tended to correctly identify pathological values but were imprecise regarding the lack of pathology.

Another evolving field in the measurement of fatigue is the measurement of different cytokines. Fatigue was partially due to how many lymphocytes are activated by the HIV. These activated lymphocytes express higher amounts of the cytokines including Tumor necrosis factor alpha (TFN-alpha) and interleukin 1 (IL-1), and have been shown to have an effect on fatigue (Kruse et al., 1995). Investigational immune-based approaches in managing the HIV disease use immune-modulating agents, such as interleukin-2 (IL-2) to augment the function of the immune system. IL-2 is a cytokine with the ability to cause widespread immune activation and the release of other cytokines, including tumor necrosis factor-alpha (TNF-alpha), gamma interferon (IFN-gamma) and

interleukin-6 (IL-6) (Dudjak, 1993). These treatments were known to cause severe fatigue, which was transient, but possibly excessive (Grady, Anderson, & Chase, 1998).

Cytokine activity is assessed by the polymerase chain reaction test (PCR). PCR is an easy and reproducible, semi-quantitative, non-radioactive method for the analysis of mRNA expression for various cytokines (i.e., interleukins such as IL-1 beta, IL-4, IL-6, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-gamma) in cells from tissue culture, cerebrospinal fluid (CSF) and peripheral blood mononuclear cells (PBMC). The intra- and inter-assay variability of the method is below 10%. With this assay, the cytokine expression pattern of as few as 10^4 mononuclear cells from blood or CSF could be determined. This method makes it possible to detect differences in the cytokine gene expression patterns of mononuclear cells. The sensitivity, specificity and reliability of this assay facilitate the analysis of cytokine production in mononuclear cells, even in conditions where only a limited number of cells are available for analysis. However, there are multiple standards for the measurement of cytokines, different epitope recognition of the antibodies used in immunoassays, and several immunoassays that bias recognition of different cytokines (Wadhwa, & Thorpe, 1998). These limitations could dramatically affect the results and need to be considered when utilized in a study.

Another important area for the indirect assessment of fatigue is the decreased levels of the gonadal hormones. Hormones in general have been described as steroids that promote and inhibit organ functions and a deficit in hormonal level could result in bodily dysfunction and experiences of physical and emotional symptoms. In HIV/AIDS, the lack of testosterone in the blood decreased energy and increased fatigue levels and was the target of many investigators (Mulligan, Tai, & Schambelan, 1998; Rabkin, Wagner, &

Rabkin, 1999). Supplementing HIV-infected men with testosterone had been proven in numerous investigations to be a valid intervention in the increase quality of life, the increase of energy, the increase of mood levels, and the decrease of fatigue (Ferrando et al., 1999; Grinspoon et al., 2000; Rabkin et al., 2000; Rabkin et al., 1999). The reliability of laboratory reproducibility of steroid hormones and sex-hormone-binding-globulin assays, however, had been called into question by substantial variability between and within laboratories (Hankinson, Manson, London, Willett, & Speizer, 1994). Again, as with most laboratory tests, the laboratory should provide sufficient information on how these tests are performed and a control test on a number of the same subjects should be performed to assure specificity and sensitivity of the test results.

Summary

The five measurement sections of fatigue in HIV/AIDS reviewed in this paper have produced several areas of interest. The newer fatigue-specific instruments are multidimensional and assess fatigue with four dimensions: Behavior/ Severity, Affective Meaning/Emotions, Sensory Changes, and Cognitive Changes (Piper et al., 1998; Schwartz, 1998). The reviewed fatigue-specific measures reported excellent validity and reliability with Cronbach's alpha as high as 0.97, which raises concerns of redundancy of the items. These measures capture well the subjective experiences of fatigue. The VAS-F, the PFS and the SCF-S have been validated in multiple studies with cancer patients but only the PFS and the VAS-F had been utilized in HIV samples. The PFS had fewer items than the SCF-S and its terminology is easier to understand. Because of the pretest of the PFS with HIV-infected gay men, the author would have had confidence in the PFS. With minor modifications to the instrument, the PFS could result in rich quantitative and qualitative data about the subjective experiences of fatigue in HIV/AIDS. Participants rated the PFS as appropriate in length, wording and that it left enough opportunities to add important qualitative information.

Symptom scales and checklists had been utilized in numerous cancer and HIV studies, and have proven to be reliable and valid research tools. The reviewed symptom checklists contain a range of 14 to 74 symptoms and ask patients to rate these symptoms for their presence, frequency and distress. The ASDS-2 and the MSAS-SF have fewer items then the SSC-HIVrev, which result in less subject burden during the completion of these instruments. However, the SSC-HIVrev is presently the most complete assessment tool in capturing symptoms in HIV/AIDS patients because of the women-specific items.

Depending on the research focus, the BDI or the CES-D depression scale could have been included in a battery of instruments to either assess frequency of depressive symptoms (CES-D) or to rate the severity of current depression (BDI). These instruments proved to be reliable and valid and both scales list a number of statements that rated on Likert scales. Neither should be used as a diagnostic tool for depression, but instead, as an assessment tool for either the depth of depression (BDI) or the frequency of depressive symptoms (CES-D). The BDI should not be utilized in fatigue research because it would yield false-positive results in HIV/AIDS research of patients with severe physical symptoms.

Since the beginning of the HIV epidemic, fatigue was identified as an important concept in quality of life measures. While the QOL-I and the MOS- SF 20 lacked a scale on fatigue and energy, developers of the MOS SF-HIV and the MOS-SF-36 integrated scales on fatigue and energy into their instruments. All of them reported good to excellent reliability and have been validated many times. However, in all measures, fatigue was only assessed for presence and absence, and the questions were mostly concerned with the distress fatigue caused the person. The 1 to 4 item scales did not give a detailed overview of the dimensionality of fatigue. Rather, they identify fatigue as a contributing factor to general health status.

Physiological measures do not directly detect fatigue, but they are of importance to researchers and clinicians. Self-reported laboratory values, values taken from medical records and actual blood tests were ways to access physiological data. Each of these methods has problems with validity, and depends on the patient's ability to recall blood-

values, on the choice and specificity of different types of tests, or on the precision of the lab technician.

CHAPTER THREE

METHODOLOGY

Research Design

This study was a descriptive, correlational, secondary data analysis. For this analysis, the original data were supported by NRSA Institutional Research Training Grant, NIH, T32NR07081; Sigma Theta Tau International – Alpha Eta Chapter; and the Texas A&M University Systems Health Science Center/Coastal Bend Health Education Center Small Grants Program. The primary study focused on the psychometric evaluation of a symptom assessment instrument for people with HIV/AIDS. A battery of instruments was administered in a survey format to investigate the relationships between HIV- related symptoms, the use of complementary therapies and quality of life.

Setting/Sample

The primary data for this secondary analysis were collected at an HIV outpatient clinic in a large urban center in Texas. The clinic was serving approximately 5,200 HIV/AIDS clients. A convenience sample of 372 HIV-infected men and women completed the study, of which 67% were men and 33% women; 73% were African-American, 15% were Caucasian, 9% were Hispanics and 1% were Native Americans. Approximately 85% of the men and women did not work (56% male vs 29% female). 12% reported their income sufficient, while 58% rated it barely enough and 30% - totally inadequate. 70% of the participants were on disability, 71% rented their homes and

60% were living with someone else. Of the 91% of the participants never received treatments for intravenous drug use with methadone, and 54% were diagnosed with AIDS.

Data Collection Methods

The participants of the original study received a questionnaire booklet, which included the following instruments: Minimum Demographic data set, CES-D, SSC-HIVrev, MOS SF-36, and the Self-Care Symptom Management Scale for People Living with HIV/AIDS. Each measurement is briefly introduced here:

1. Minimum Demographic Data Set.

The demographic questionnaire included self-report questions pertaining to age, gender, ethnicity, level of education, number of children, living situation, insurance coverage, employment, recreational drug use, CD4 count, and viral load, number of years of HIV diagnosis, history of AIDS-related hospitalizations and adequacy of income.

2. The Center of Epidemiological Studies Depression Scale (CES-D).

This 20-item scale is a non-diagnostic screening tool for depressive symptoms experienced within the last week (Radloff, 1977). Item responses range from 0 (never or rarely) to 3 (mostly or all of the time), with a total score range from 0 to 60. Any score above 15 would indicate the need for a diagnostic evaluation of major depression. The alpha reliability estimate was 0.90 in a sample of 727 AIDS

patients (Holzemer et al., 1999).

3. The Revised Signs and Symptoms Checklist for Persons with HIV disease (SSC-HIVrev).

The SSC-HIVrev is a 74-item checklist that assesses the presence and intensity of signs and symptoms commonly experienced by people with HIV/AIDS in a 24-hour period (Holzemer et al., 1999, Holzemer et al., 2001). The SSC-HIVrev includes 74 signs and symptoms, rated on an ordinal 3-point Likert scale (mild, moderate, or severe). The alpha reliability coefficients for the factor scores ranged from 0.79 to 0.90 in a sample of 372 HIV/AIDS patients (Holzemer, et al., 2001).

4. The Medical Outcomes Study: Short Form-36 (MOS SF-36).

The MOS SF-36 is a well-established quality of life measurement scale used with many different populations (healthy, acutely, and chronically ill samples) (Ware & Sherbourne, 1992). The MOS SF-36 contains nine subscales: physical functioning, role-physical, role-emotional, bodily pain, social functioning, mental health, general health perception, vitality, and changes in health. Multiple studies established validity and reliability of the subscales (Aaronson et al., 1992; McHorney et al., 1994; Wagner et al., 1998). The original scores ranged from yes or no, 0 to 3, 0 to 5, and 0 to 6, depending on the subscale. All of the original scores were converted to a 0 to 100-point scale, with 100 being perfect health and 0 – poorest.

5. Self-Care Symptom Management Scale (SCSMS) for Living with HIV/AIDS. This instrument was used in a Web-based study to investigate self-care management of HIV symptoms (www.hivsymptoms.com). In an open-ended format, subjects were asked to identify physical and psychological symptoms they frequently experienced in a period of one month. They were requested to describe these symptoms and to rate symptom intensity, distress, and impact on their daily lives. The 6 most commonly identified symptoms in men and women with HIV/AIDS were: anxiety/fear, nausea/vomiting, depression, neuropathy, fatigue and diarrhea. Based on the symptoms, the participants were asked to identify strategies used to manage each symptom. The study team grouped the self-care behaviors and fatigue management strategies that were developed for all six symptoms. Among those were: relaxation, breaks, walk, consumption of more natural food and avoidance of alcohol and caffeine, development of a sleep routine, and use of prescribed medications.

Procedure and Protection of Human Subjects

The study was explained to all patients who came to the clinic for their regular appointments and volunteered in the study. They were informed their participation would not affect their future quality of care at the clinic. The only potential risks for them were: privacy loss, confidentiality loss, or a feeling of discomfort as a result of filling out the questionnaire. Upon completion of the questionnaire, which took approximately 45 minutes to complete, the subjects were paid $10 for their participation. Under the rules and regulations of the University of California, San Francisco, and the Harris County 5 Hospital District, Houston, Texas, a signed consent form was obtained from every

subject. Subjects were provided with copies of the consent form and the Experimental Bill of Rights (see Appendix 1).

Data Analysis and Aims

All data were double entered and cleaned after being checked for outliers and errors. The data were analyzed using SPSS Statistical Package version 11.0 (SPSS Inc., Chicago, IL). Analyses were delineated for each of the study aims as followed:

Aim 1: Describe the intensity of fatigue as influenced by selected person, environment, and health and illness variables. **Analysis:** Selected variables were analyzed using t tests and ANOVA for fatigue intensity. Continuous variables were correlated with fatigue using Pearson's correlation coefficient. For these analyses, the SSC-HIVrev fatigue factor score were utilized (range 0-12). The factor was composed of 4 items on a mild-moderate-severe scale, and measured intensity of fatigue, muscle aches, weakness and painful joints for the present day.

Aim 2: Explore the potential confounding of fatigue and depression through an analysis of convergent and divergent correlations and known-group differences. **Analysis:** The number of items on the scale, Cronbach's alpha, means, standard deviations, and correlations for the two measures of fatigue (SSC-HIVrev fatigue factor score, SCSMS fatigue), one measure of vitality (MOS-SF36 vitality scale), and the three measures of depression (SSC-HIVrev depression factor score, SCSMS depression, CES-D) are presented in a table. Campell and Fisk's multi-method/multi-trait correlation analysis (1959) were be utilized to explore convergent and divergent validity between the scales of fatigue with vitality, fatigue with depression, and vitality with depression. The

correlation matrix provides information about the strength and the direction of the correlation among the fatigue, vitality and depression measures. The predicted relationships exploring convergence and divergence are recorded in Table 2. Construct validity for the SSC-HIVrev fatigue factor score were established by the Known-Group Difference method, where a critical attribute (mild-moderate-severe fatigue ratings) was expected to vary, compared to known characteristics such as vitality and depression scores. ANOVA was used to confirm the hypotheses for the Known-Group -Difference method. Differences in fatigue and depression were explored by gender, age and CD4 count.

Table 2. Campell and Fisk Multi-Method/Multi-Trait Correlation Matrix

	Vitality	Fatigue		Depression		
	MOS-SF36	HIV-SSC	SCSMS	HIV-SSC	SCSMS	CES-D
MOS-SF36	$r_{1,1}$ = high	$r_{1,2}$ = moderate	$r_{1,3}$ = m oderate	$r_{1,3}$ = moderate	$r_{1,4}$ = ,medium	$r_{1,4}$ = medium
HIV-SSC		$r_{2,2}$ = high	$r_{2,3}$ = high	$r_{2,3}$ = medium	$r_{2,4}$ = medium	$r_{2,4}$ = medium
SCSMS			$r_{3,3}$ = high	$r_{3,3}$ = medium	$r_{3,4}$ = medium	$r_{3,4}$ = medium
HIV-SSC				$r_{3,4}$= high	$r_{4,4}$ = high	$r_{4,4}$ = high
SCSMS					$r_{4,5}$= high	$r_{4,5}$= high
CES-D						$r_{5,6}$= high

Proposed Relationships

1. A moderate negative relationship was expected between the MOS SF-36 vitality scale and the two fatigue scales.
2. A high positive relationship was expected between the SSC fatigue factor score and the SCSMS fatigue score.
3. A high positive relationship was expected between the SSC-HIVrev depression factor score, the SCSMS depression score, and the CES-D depression.
4. A moderate positive relationship was expected for the three depression measures with the fatigue measures.
5. A moderate negative relationship was expected between the MOS SF-36 vitality scale and the three depression measures.

Aim 3: To test the UCSF-SMM through exploring the contribution of fatigue on the physical and mental health of patients with HIV/AIDS. **Analysis:** First, to test the UCSF-SMM, a correlation matrix would correlate fatigue with all 18 variables in order to determine the strength and the direction of the relationships. Second, a number of multiple regression models with block-wise entry of the independent variables were conducted, in order to determine the individual contributions of that particular block to fatigue. According to the UCSF-SMM, the proposed blocks are: person variables (age, gender, ethnicity, completed high school education, completed college education, disability, drug use); environment variables (income, insurance); health and illness variables (years known HIV diagnosis; years known AIDS diagnosis, CD4 cell count, viral load); and symptom variables (fatigue, depression, shortness of breath, diarrhea, and lipodystrophy). Third, in order to determine the impact of fatigue on the physical and mental health as sub-concepts of quality of life, the MOS SF-36 subscales were divided into a physical and a mental health score. Composite physical and mental health scores were utilized as dependent (outcome) variables to explore the contribution of fatigue to physical and mental health within the concepts of the UCSF Symptom Management. Finally, two hierarchical regression models with block-wise entry of the independent variables were conducted, examining the contribution of fatigue on the predictors and correlates of physical and mental health.

CHAPTER FOUR

RESULTS

Aim 1: Describe the intensity of fatigue by selected person, environment, and health and illness variables.

The first aim was to describe the intensity of fatigue by selected person, environment and health and illness variables. To address the first aim, data were included from 372 subjects with HIV/AIDS in an outpatient clinic in Texas. On the SSC-HIV fatigue scale, the mean fatigue score was 5.7, ± 3.6, with a range of 0-12; 12% rated fatigue as 0, 30% rated fatigue as 1-4 or mild, 31% rated fatigue as 5-8 or moderate, and 27% rated fatigue 9-12 or severe. On the SCSMS fatigue (n=144), the mean fatigue score was 22.0, ± 10.1, with a range of 4-37; 21.5% rated fatigue as 4-12 or mild, 37% rated fatigue as 13-24 or moderate, and 41.5% rated fatigue as 25-37 or severe (see Table 5).

The mean age was 39.9 years (see Table 3). The gender distribution was representative for the national distribution for HIV/AIDS cases in the United States (CDC, 2001), 32% were female. Most of the participants (73%) were African-American, 15% were Caucasians and 9% were Latinos (see Table 3), which was disproportionately higher in African-Americans than the US average (50%) (CDC, 2001). The final 3% consisted of 1 Asian, 4 Native Americans, and 6 people not ethnically identified. While 59% of the participants did not finish high school, 39.5% received a high school degree, and 12% held a college degree. Almost 70% of the men and women considered themselves disabled, and 56.7% reported a totally inadequate income. Only 29%

stated that their health insurance was sufficient for their healthcare needs, while 71% rated their insurance situation poor or inadequate. The majority lived in rental properties (60% did not live alone, 45% had children, and 85% were unemployed).

The year of HIV infection was unknown by 53% of the participants (see Table 3). Of those who identified the year of HIV infection, 7.3% reported they were infected between 1982-1990, and 39.7% between 1991-2000. Knowledge of the year of AIDS diagnosis differed greatly from the time of HIV infection; 91.6% of respondents reported their current AIDS status, of which 54% identified themselves having AIDS, and 8%, did not. CD4+ cell count was known by 42%, who had a mean CD4+ T cell count of 452 mm^3, a standard deviation of 315 mm^3 and a range from 2 to1800 CD4+ cells. Only 42% of the subjects knew their viral load values with a mean of 44,893 copies, a standard deviation of 166,688 copies, and a range from 0 to1 million viral copies.

Intensity of fatigue was estimated with the SSC-HIV fatigue factor score. Differences in fatigue intensity scores by person, environment, and health/illness variables were explored (see Table 3). The following significant differences were noted. Women reported more fatigue than men. Disabled individuals reported more than their counterparts. Those individuals with inadequate income and CES-D scores >15 reported more fatigue. Those individuals with adequate health insurance, who worked for pay reported less fatigue. Those individuals who lived alone experienced less fatigue.

Age, CD4+ cell counts, and viral load were correlated with fatigue as continuous variables (see Table 4), and did not show significant differences for different intensity levels of fatigue.

Table 3. SSC-HIV Fatigue Intensity Scores according to Person, Environment and Health/Illness Variables in a Sample of Persons Living with HIV/AIDS (N=372)

Variables	N	Percent	Mean Fatigue Intensity	SD	t/F	df	p value	Post-hoc analysis
Gender					t=2.11	366	< .04	
Female	118	31.7	6.25	3.70				
Male	250	67.2	5.40	3.58				
Missing	4	1.1						
Ethnicity					F=3.98	2	<.001	All comparisons not significant using Scheffe
African American	271	72.8	5.30	3.52				
Hispanic/Latino	33	8.9	7.09	3.63				
Caucasian	55	14.8	6.61	3.72				
Others	11	3.0	5.90	4.36				
Missing	2	0.6						
Education					t= 1.45	366	0.15	
High School	221	39.5	5.97	3.56				
No High School Degree	147	59.4	5.41	3.6				
Missing	4	1.1						
College Degree					t= 0.42	336	0.68	
Yes	45	12.1	5.77	4.10				
No	293	78.8	5.53	5.77				
Missing	34	9.1						
Disabled					t= -3.00	361	<.001	
Yes	259	69.6	6.08	3.62				
No	104	28.0	4.84	3.51				
Missing	9	2.4						
Housing					F=1.11	2	0.33	All comparisons not significant using Scheffe
Rent	264	69.9	5.60	3.69				
Own	25	71.0	6.72	3.20				
Other	81	6.7	5.68	3.61				
Missing	2	0.5						
Income					F= 7.82	2	<.001	All comparisons significant using Scheffe
Enough	46	21.8	4.24	3.14				
Barely Enough	211	12.4	5.47	3.62				
Totally	112	56.7	6.59	3.63				
Missing	3	0.8						

Insurance					F= 4.42	2	0.01	All comparisons significant using Scheffe
Enough	107	28.8	4.81	3.5				
Barely adequate	146	39.2	6.10	3.5				
Totally Inadequate	113	30.4	6.00	3.8				
Missing	6	1.6						
Living Status					t= -1.85	369	0.06	All comparisons significant using Scheffe
Do not live alone	223	59.9	5.95	3.5				
Live alone	148	39.8	5.23	3.7				
Missing	1	0.3						
Children					t= 0.59	368	0.56	
No children	202	54.3	5.57	3.5				
Children	168	45.2	5.79	3.8				
Missing	2	0.5						
Employment					t= 1.94	370	0.05	All comparisons significant using Scheffe
Unemployed	315	84.7	5.83	3.6				
Employed	57	15.3	4.82	3.4				
Year of HIV Diagnosis					t= 0.29	349	0.76	
1975-1990	82	23.4	5.85	3.5				
1991-2000	269	76.6	5.72	3.6				
Missing	197	53.0						
Year of AIDS Diagnosis					t= 0.21	173	0.83	
1982-1990	27	15.4	6.00	3.2				
1990-2000	148	76.6	5.83	3.7				
Don't know	30	8.1						
Hospitalized in Past 12 months					t= 1.43	369	0.15	
Yes	88	23.7	6.15	3.6				
No	283	76.1	5.51	3.6				
Missing	1	0.3						

History of Drug Use					F= 3.16	2	0.04	All comparisons not significant using Scheffe
Former	134	36.0	6.23	3.62				
Never	225	60.5	5.31	3.57				
Current	10	2.6	6.80	4.76				
Missing	3	0.9						
Depressed (CES-D)					t= -4.17		<.001	
No <16	46	12.4	3.65	3.25				
Yes> 15	325	87.6	5.98	3.58				

Table 4. Correlations between Continuous Person and Health/Illness Data and the SSC-HIV Fatigue Intensity Scores

Variables	N	M	SD	Range	r	p
Age	372	39.9	8.3	18-66	0.01	0.79
CD4 value	157	452	315	2-1800	-0.10	0.21
Viral load value	125	44,893	166,688	0-1 million	0.03	0.77

Aim 2: Explore the potential confounding of fatigue and depression through an analysis of convergent and divergent correlations and known-group differences.

The second aim explored the potential confounding of fatigue and depression and provided an opportunity to evaluate construct validity (convergent/divergent). Data were included from the CES-D for depression information, the MOS SF-36 subscale for vitality, the SSC-HIVrev for fatigue and depression data, and fatigue and depression data from the symptom rating scale of the Self-Care Symptom Management Scale (SCSMS). Besides the SCSMC, all other instruments had established reliability and validity data in previous studies. Before exploring the confounding, the reliability and the validity of the subscales were re-evaluated to confirm previous findings concerning each instrument or subscale.

1. The CES-D is a 20-item scale, utilized as a non-diagnostic screening tool for depressive symptoms. It measured frequency of depressive symptoms over a period of one week (Radloff, 1977). In this study, 371 men and women with HIV/AIDS completed the CES-D. Cronbach's alpha reached 0.88, indicating an excellent internal consistency among the items. It confirmed previous findings that the scale was a reliable instrument in measuring the frequency of depressive symptoms in HIV/AIDS samples.

2. The MOS SF-36 is a 36-item instrument measuring the quality of life in 9 different subscales: physical functioning, role functioning, emotional functioning, bodily pain, general health, vitality, social functioning, and mental health. The reliability coefficient for the vitality scale was a moderate 0.69 (N=368) (see Table 7). An overview of the

reliability coefficients of the nine instrument scales can be found in Appendix 6. Cronbach's alpha ranged between 0.89 for physical functioning and 0.58 for social functioning. To calculate the physical and mental health summary scores, three subscales of the MOS- SF36 were summed and divided by 3, including physical functioning, role functioning, and social functioning. Four subscales of the MOS-SF 36 were summed and divided by 4, to measure mental health, including general health perception, emotional functioning, health transition and mental health

3. The SSC-HIVrev is a 74-item list of the most common symptoms in HIV/AIDS disease, 8 of which are women-specific. On the day the scale was completed, the checklist evaluated the presence and the intensity of each symptom on a 3-point scale (mild - moderate - severe). Internal consistency for a symptom checklist could not be established because of the multiple concepts nature of the scale. However, in order to evaluate the reliability of groups of symptoms, a factor analysis was conducted and symptoms were grouped according to their clusters. This work had been published in a previously (Holzemer et al., 2001). The 4-item factor cluster for fatigue (fatigue, muscle aches, painful joints and weakness) and the 4-item factor cluster for depression (difficulty concentrating, depression, memory loss, and fear/worries) were evaluated for a reliability coefficient. Both factors had excellent internal consistency with 0.86 for fatigue and 0.87 for depression, indicating a strong internal consistency between the items.

4. Self-Care Symptom Management for Living with HIV/AIDS. This instrument was developed for a Web-based study to investigate self-care management strategies of

HIV symptoms (www.hivsymptoms.com). In an open-ended format, subjects were asked to identify physical and psychological symptoms that they frequently experienced. They were requested to describe these symptoms and to rate them based on duration (1 to 7 days of the past week), intensity (1 to 10 from very low to very high), distress (1 to 10 from very low to very high), and the degree to which it affected their daily lives (1 to 10 from very low to very high). The 6 most commonly identified symptoms were: anxiety/fear, nausea/vomiting, depression, neuropathy, fatigue, and diarrhea. Cronbach's alpha was calculated for both scales and the reliability coefficient for the fatigue scale reached 0.92, indicating a strong coherence between the items. The reliability coefficient for the depression scale was 0.92, an equally strong indicator for internal consistency between the depression items.

Known Group Differences

To analyze the construct validity of the SSC-HIVrev fatigue factor, the score was compared to the MOS SF-36 vitality score and the CES-D depression score, using the known-group difference method. In this type of analysis, three groups were expected to vary on the critical attributes (vitality or depression) because of some known characteristics. In this case, the known characteristics were the fatigue factor scores grouped into high-moderate-low ratings (see Table 5). A one-way ANOVA explored potential differences. These groups were compared using the vitality score of the MOS SF-36 and the depression score of the CES-D. Evidence for the construct validity of the SSC-HIVrev fatigue factor score was established when the vitality scores decreased with increasing fatigue, or when the CES-D depression scores increased with increasing fatigue scores. The data in Tables 5 and 6 provided the evidence for construct validity of the SSC-HIVrev fatigue factor score. With increasing fatigue ratings, the vitality scores decreased, and the CES-D scores increased. These group differences were highly significant and established evidence for the construct validity for the SSC-HIVrev fatigue factor score. Post hoc tests revealed that all group comparisons of vitality and fatigue were significantly different, and that the groups of the mildly and severely depressed and the moderately and severely depressed were significantly different.

Table 5. Mild-Moderate-Severe SSC-HIVrev Fatigue Scores compared to the MOS SF-36 Vitality Score and the CES-D Depression Total Score

	Grouped SSC-HIVrev Fatigue Scores							
MOS SF-36 Vitality Score (n=368)	Mild M	SD	Moderate M	SD	Severe M	SD	Total M	SD
Total	66.03	20.38	49.33	16.59	32.30	16.86	51.98	17.32
CES-D Score (n=368)								
Total	24.52	10.96	28.31	10.00	33.96	10.31	28.12	10.63

Table 6. Two-way ANOVA for Severity of SSC-HIVrev Fatigue Scores by CES-D Total Score and MOS-Vitality Score

ANOVA	Mean Square	df	F	p
CES-D	2488.01	1,368	22.74	< 0.001
Vitality	32269.62	2,368	95.38	< 0.001

Confounding Effects of Fatigue and Depression

There has been a longstanding debate on whether fatigue and depression were separate or similar concepts, but viewed from different perspectives. The mean score for the SSC-HIVrev fatigue factor score with a range of (0-12) was compiled in Table 7, by dividing the SSC-HIV fatigue score into 3 groups: mild (0-4), moderate (5-8), and severe (9-12). The overall mean score was 5.7 and fell in the moderate range. The SCSMS score ranged from (0-37) and was divided into 3 groups: mild (0-13), moderate (14-26), and severe (27-37). The average mean score was 22.0 and it was also in the moderate range. Both measures detected the same intensity of fatigue in men and women. The MOS SF-36 vitality score ranged from 0 to 100 and it was divided into mild (0-33), moderate (34-66), and severe (67-100). The mean score of vitality was 52.0 and once again fell in the moderate range. In the depression scores, the SSC-HIVrev depression factor score ranged from 0 to 12. The mean score was 5.7, and like the fatigue scores, it fell into the moderate score range. The SCSMS' mean depression score was 22.3, and also in the moderate range. However, the CES-D mean score was 28.1, and it fell in the severe range, confirming previous research (Perdue et al., 2003). Usually, any score of 16 or higher would prompt a healthcare provider to screen for clinical depression.

Fatigue and vitality have often been discussed as a person's contrary ends of a continuum of energetic states (Lee et al., 1991, 1994). While in general, vitality represented one's life energy necessary to perform daily activities; fatigue represented one's state at the end of a tiring day with a need to replenish the depleted energy reservoirs. By correlating the two fatigue scales with the vitality scale as part of the divergent validity assessment, it was hypothesized that there should be significant

correlations in the reverse direction (see Table 7). The score for the MOS vitality scale correlated with the SSC-HIVrev fatigue factor score ($r = -0.50$, $p<.001$) and with the SCSM fatigue scale ($r = -0.42$, $p<.001$). It indicated that fatigue and vitality were indeed significantly and inversely related. These inverse relationships were an indicator for divergent validity. The SSC-HIVrev fatigue score and the SCSM fatigue scale correlated ($r = 0.45$, $p<.001$) and provided further evidence that these two measures were moderately related. Although the relationships were not as strong, they indicated a convergent validity between the two measures.

The scores for the three depression measures all correlated positively with each other, providing some evidence for convergent validity of depression as the underlying concept. The SSC-HIVREV depression score and the SCSM depression score correlated ($r = 0.60$, $p<.001$), the SSC-HIVrev depression score and the CES-D total score correlated ($r = 0.45$, $p<.001$), and the SCSM depression score and the CES-D correlated ($r = 0.46$, $p<.001$).

The final questions were concerned with the variance that was shared by depression and fatigue, depression and vitality, as well as, whether fatigue and depression were conceptually the same or different. Some overlap in the measurements of fatigue and depression were expected. Depression was mostly accompanied by physical symptoms such as fatigue and insomnia, when persisted for a longer periods of time. Similarly, when fatigue was present over a period of several months, it also affected negatively the mood states and sleep. Moderate correlations were expected between the scores of the CES-D as a screening tool for depressive symptoms and the two fatigue measurements. Correlating the CES-D score with the SSC-HIVrev fatigue score, a weak

relationship was found ($r = 0.34$, $p < .001$). A weak relationship was also found between the CES-D total score and the SCSMS fatigue score with a correlation of ($r = 0.29$, $p < .001$), indicating that the items in the three measurements detected two distinct concepts. However, moderate relationships were found between the SSC-HIVrev factor scores of fatigue and depression ($r = 0.61$, $p < .001$). Equally strong relationships were detected between the SCSM subscales for fatigue and depression ($r = 0.64$, $p < .001$). The moderate relationships indicated a greater conceptual overlap between the items of depression and fatigue for these four subscales.

In general, all of the measures were significantly correlated in the range of .28- .64 at p values less than .001. The highest shared variance ($r = .64$; $r^2 = 40.9\%$) demonstrated that Self-Care fatigue and Self-Care depression shared only 41% common variance. The SSC-HIV fatigue factor score and the CES-D total score were selected to be the utilized in the multiple regressions.

Table 7. Descriptive Statistics and Correlations for Measures of Fatigue, Vitality and Depression

Measures	N	# of Items	Mean	SD	Cronbach alpha	SSC-Fatigue	SC-Fatigue	SF36 Vitality	SSC-Dep	SC-Dep	CES-Dep
Fatigue											
SSC-Fatigue	372	4	5.68	3.63	0.86		.43*	-.58*	.63*	.42*	.33*
Self-Care-Fatigue	144	4	21.99	10.11	0.92			-.42*	.48*	.64*	.28*
SF-36 Vitality	369	4	51.98	22.62	0.69				-.55*	-.45*	-.41*
Depression											
SSC-Depression	372	4	5.57	3.64	0.87					.57*	.49*
Self-care-Depression	157	4	22.29	9.34	0.92						.45*
CES-D Depression Total	371	20	28.13	11.06	0.88						

*All correlations are significant at p<.001

Several t tests and analyses of variance were conducted to further explore potential confounding variables of fatigue and depression, as well as, to establish whether fatigue and depression operated in the same way across the gender groups. Gender ratings were compared to the two fatigue scales, the vitality scale and the three depression scales (see Table 8). The mean fatigue scores of the SSC-HIVrev fatigue factor score were higher for women than for men ($t = 2.11$, $p < .04$). No significant mean score differences were found for the SCSMS fatigue score and the MOS SF-36 vitality score between men and women. Women scored higher than men on the SSC-HIVrev depression factor score ($t = 2.26$, $p < .02$) and the CES-D total score ($t = 2.37$, $p < .02$). The SCSMS depression scores were not different for men and women.

Table 8. Gender Differences in Fatigue and Depression

Variables	Gender	N	Mean	SD	t	df	p
Fatigue							
SSC-Fatigue	female	118	6.25	3.70	2.11	366	.035
	male	250	5.40	3.58			
Self-Care Fatigue	female	51	22.67	10.15	0.673	140	.502
	male	91	21.47	10.14			
MOS SF-36 Vitality	female	117	49.84	23.31	-1.22	363	.224
	male	248	52.94	22.41			
Depression							
SSC-Depression	female	118	6.19	3.73	2.26	366	.024
	male	250	5.27	3.57			
Self-Care Depression	female	52	23.35	9.86	1.02	153	.310
	male	103	21.72	9.14			
CES-Depression	female	118	30.14	12.54	2.37	365	.019
	male	249	27.22	10.26			

Previous researchers proposed age to be a predictor of fatigue (Singh et al., 1997; Cjederfall et al., 2001). For this study, age ranged between 18 to 66 years, with a mean age of 39.9 and a standard deviation of 8.3 years. Several additional tests were conducted to further explore age as a potential confounding variable for fatigue and depression. Age as a continuous variable was compared to the SSC-HIVrev fatigue factor score ($r= 0.01$, $p<.79$) and the SCSMS fatigue score ($r= -0.08$, $p< .31$), and the mean differences for both scores were statistically insignificant. According to literature, higher fatigue scores were found in people with HIV/AIDS ages 35 and older (Singh et al., 1997); (Cederfjall et al., 2001) and in men 42 years and older. In the study group, 47.1% of the participants were 40 years and older. According to the mean age of the study's participants, two groups were created: 40 years and younger, and 41 years and older. The analysis of fatigue, depression scores and age, did not reveal significant differences in the SSC-HIVrev fatigue factor score ($t= .107$, $p<.91$), the SCSMS fatigue score ($t= 1.2$, $p<.21$) or the MOS SF-36 vitality score ($t= .90$, $p= 0.36$). Likewise, no differences were found for the two age groups in the SSC-HIVrev depression score ($t= .31$, $p<.75$), the SCSMS depression score ($t= -.13$, $p<.89$), or the CES-D total score ($.05$, $p<.96$) (see Table 9).

Table 9. Age (under and over 40) Differences in Fatigue and Depression

Variables	Age	N	Mean	SD	t	df	p
Fatigue							
SSC-Fatigue	<=40	192	5.66	3.61	0.107	361	.915
	>40	171	5.62	3.63			
Self-Care Fatigue	<=40	65	23.09	11.08	1.244	138	.216
	>40	75	20.97	9.05			
SF-36 Vitality	<=40	192	53.27	22.69	0.907	358	.365
	>40	168	51.12	22.15			
Depression							
SSC-Depression	<=40	192	5.63	3.70	0.315	361	.753
	>40	171	5.50	3.61			
Self-Care Depression	<=40	77	22.10	9.55	-0.137	152	.891
	>40	77	22.31	7.56			
CES-Depression	<=40	192	28.15	10.35	0.053	360	.958
	>40	170	28.09	8.35			

Finally, fatigue and depression were explored by different levels of CD4 counts (see Table 10). Participants were divided into three groups: > 500 CD4 cells, 200-500 CD4 cells, or < 200 CD4 cells. The 3 groups of CD4 counts corresponded to the common practices in HIV care. Those with CD4 counts < 200 were typically invited to take antiretroviral medication and were carefully monitored. Those > 500 were usually not recommended to take HIV medications, unless they had experienced an opportunistic infection. The following questions were asked:

1. Do people with HIV/AIDS with more than 500 $CD4^+$ T cells report mild fatigue or depression or none?
2. Do people with HIV/AIDS with 200 to 500 $CD4^+$ T cells report moderate fatigue or depression?
3. Do people with HIV/AIDS and with below 200 $CD4^+$ T cell counts report severe fatigue or depression?

The results were compiled in Table 10 displaying the values of fatigue, vitality and depression scores for the three groups. The mean scores for the SSC-fatigue decreased with increasing CD4 cell counts, which was also true for the SCSMS fatigue scores. This observation would have answered the three questions relating to fatigue intensity. The MOS SF-36 vitality score was the highest for the group with over 500 CD4 cells and the lowest for the group with 200-500 CD4 cells. However, none of these mean differences were statistically significant. Depression scores for the SSC-HIVrev depression scale decreased with increasing CD4 cell counts. However, the mean differences were small and statistically not significant. The SCSMS depression score did not vary for the three groups. The CES-D had equally

high scores for the groups below 200 CD4 cells, and the group between 200-500 CD4 cells. However, the group above 500 CD4 cells was 3 points lower, which was considered an insignificant difference.

Table 10. CD4 Levels and Fatigue and Depression

Variables	CD4	N	Mean	SD	F	df	p	Post-hoc Comparisons
Fatigue								All comparisons not significant using Scheffe
SSC-Fatigue	<200	34	5.94	3.77	1.358	2,154	.260	
	200-500	70	5.51	3.71				
	>500	53	4.68	3.69				
Self-Care Fatigue	<200	12	24.08	9.32	0.642	2,63	.530	
	200-500	36	23.58	10.12				
	>500	18	20.50	11.35				
SF-36 Vitality	<200	34	51.72	22.44	1.024	2,154	.362	
	200-500	68	49.29	24.22				
	>500	53	55.38	22.40				
Depression								
SSC-Depression	<200	34	5.56	4.02	0.266	2,154	.767	All comparisons not significant using Scheffe
	200-500	70	5.46	3.78				
	>500	53	5.02	3.93				
Self-Care Depression	<200	16	22.31	11.01	0.094	2,65	.911	
	200-500	36	23.31	9.54				
	>500	22	22.36	8.45				
CES-Depression	<200	34	28.12	9.62	0.954	2,154	.388	
	200-500	69	28.07	11.50				
	>500	53	25.70	8.74				

Aim 3: To test the UCSF-SMM by exploring the contribution of fatigue to the physical and mental health of patients with HIV/AIDS.

To evaluate Aim 3, variables were selected according to the previous findings and the major concepts of the UCSF symptom management model. The major concepts were person, environment, symptom perception, health and illness, and quality of life. Three major steps were necessary to develop the final hierarchical regression models. First, all variables were entered into a correlation matrix to evaluate the strength and direction of the inter-correlations between the different variables. Second, the theoretical block variables were entered in separate blocks to understand the strength of the relationships between them and fatigue. The final hierarchical regression models encompassed three blocks to investigate the independent contributions of fatigue intensity and depression to physical and mental health while holding all other variables constant.

As the final fatigue measure, the SSC-HIVrev intensity fatigue factor score was selected as one of the independent variables. The following person variables were entered: gender, age, high school and college education, ethnicity, drug use, and disability. Income and health insurance were entered as environment variables. The following symptom variables were entered: fatigue, depression, shortness of breath (SOB), diarrhea and lipodystrophy. The following quality of life variables were entered: physical functioning, emotional and physical role functioning, health perception, social functioning, emotional functioning, and health transition. The health and illness variables were: CD4+ cell count, viral load, time since HIV infection in years, and time since AIDS diagnosis in years. Every selected variable was entered into a correlation matrix

(see Appendix 7). Fatigue intensity correlated weakly with gender, income, race, disability and drug use (between r= 0.11 to r=0.17, p< .05). A weak correlation was found also between fatigue and depression (r=0.33, p< .01), but moderate correlations were found between fatigue and SOB (r= 0.62, p=<.01), diarrhea (r= 0.59, p<.01), and lipodystrophy (r= 0.48, p< .01). Pain, a significant predictor of fatigue, was not entered as separate variable because some of the factor scores, such as SOB and diarrhea already included pain ratings for abdominal and chest pains. Fatigue correlated with all subscales of the MOS SF-36 between (r= 0.24) for health transition and (r= 0.44, all of them at p<.01). The duration of HIV/AIDS, CD4 values and viral load values did not correlate significantly with fatigue.

The next step of the analysis determined the block variables for the final hierarchical multiple regression models, and four blocks were identified. Each block was entered separately as a multiple regression to investigate the independent contributions of these variables to fatigue (see Table 11). In the person block, age, gender, high school degree, college degree, ethnicity, disability, and drug use were entered as potential independent contributors to the ratings of fatigue.

Table 11. Five Separate Regressions of Fatigue on Predictors in Five Domains

Fatigue	**N**	**R^2**	**sr^2**	**Df**	**F**	**p**
Person	N=317	.099		7,332	4.846	<.000
Age			.00			
Gender			.00			
College			.00			
High School			.00			
Disability			.01*			
Drug User			.02*			
Ethnicity			.03*			
Environment	N=364	.030		2,361	4.932	<.008
Insurance			.00			
Income			.02*			
Health/Illness	N=37**	.002		4,32	.185	.945
HIV Duration			.00			
AIDS Duration			.00			
CD4 Value			.00			
Viral Load Value			.00			
Symptoms	N=369	.474		4,368	80.380	<.000
Depression			.01*			
SOB			.10*			
Diarrhea			.06*			
Lipodystrophy			.03*			
Quality of Life	N=364	.301		7,356	21.874	<.000
SF-36 Physical Functioning			.02*			
SF-36 General Health			.02*			
SF-36 Role Functioning			.02*			
SF-36 Emot. Functioning			.00			
SF-36 Social Functioning			.00			
SF-36 Mental Health			.02*			
SF-36 Health Transition			.00			

* sr2 was significant at the .05 level. ** significant drop due to missing data

Disability, drug use, and ethnicity, together explained 9.9% of the total variance in fatigue. Gender, education and age were not significant person variables. For the environment block, sufficient health insurance and level of income was entered and explained 3.0% of the total variance in fatigue, and income became a significant predictor. For the health and illness block four variables were entered: duration of HIV infection, duration of AIDS diagnosis, $CD4^+$ cell counts and viral load values. The numbers for these variables dropped significantly due to great amounts of missing data. Therefore, none of the health and illness variables were entered into the later hierarchical regression models. Combined, these four variables accounted for 0.02% of the total variance in fatigue.

The symptom perception block encompassed four symptoms. There was established evidence that linked depression, SOB, diarrhea, and lipodystrophy to the development of fatigue, and 47% of the total variance in fatigue was explained by the presence of depression, shortness of breath, diarrhea, and lipodystrophy. All four symptoms were predictors of fatigue, where SOB was the strongest predictor with 10%, followed by diarrhea with 6%, lipodystrophy with 3%, and depression with 1%.

The quality of life block included seven subscales from the MOS SF-36: physical functioning, general health perception, role physical functioning, role emotional functioning, social functioning, mental health and health transition. Vitality was excluded from this analysis because of the overlap with fatigue. The seven components together, accounted for 30.1% of the total variance in fatigue in men and women with HIV/AIDS. Physical functioning, role physical functioning, general health perception, and mental health, each accounted for 2% of the variance in fatigue.

In order to test the UCSF-SMM, a conceptual shift was necessary for this final analysis. Fatigue was correlated with a number of indicators of mental and physical health, proving a connection but not causation between physical and mental indicators that contributed to fatigue. Fatigue previously predicted the extent of quality of life. In the UCSF-SMM quality of life should be predicted by the symptom ratings. Therefore, a decision was made that instead of attempting to predict fatigue by the joint physical and mental components of quality of life, the quality of life scales were sub-divided into two separate scores: one for physical and the other for mental health. These two composite scores became the dependent variables for the following hierarchical regression models. Person, environment, and symptom variables, including the SSC-HIVrev fatigue intensity score and the CES-D total score, were regressed on either the physical or the mental health composite scores. The physical health composite score encompassed three subscales of the MOS SF-36: physical functioning, role functioning, and social functioning. The composite mental health score combined four subscales of the MOS SF-36: general health perception, emotional functioning, health transition, and mental health.

Hierarchical Regression Models

A mix of methods of multiple and hierarchical regression models were chosen in order to answer study Aim 3 and identify predictor variables for physical and mental health outcomes in HIV/AIDS. Multiple regression models evaluated the contributions of the independent variables on the dependent variables. However, the relationships between the four concepts could not be assessed at this time. Next in the statistical analysis, hierarchical regression was a useful tool for testing those relationships to extract data by entering the independent variables cumulatively in a pre-sequenced order (Hazard Munro, 2001, p.264). The pre-sequenced order was determined by the information gathered through literature, as well as the theoretical framework. In an attempt to evaluate the predictors for physical and mental health separately, three model blocks represented the final model. Subsequently, the physical and mental health became the outcome variables representing quality of life. The person block included all variables used in previous regression models such as disability, ethnicity and current drug use. The second block encompassed the environment variables such as income and insurance. In the last block, symptom intensity scores from the SSC-HIVrev such as fatigue, shortness of breath, diarrhea, lipodystrophy were considered as well as the CES-D total score for depression. Physical and mental health was evaluated in a two-step approach. The first step involved the assessment of the independent blocks of variables for the person, environment, health/illness and symptom blocks relating to physical and mental health. The second step involved 2 hierarchical regression models for both dependent variables.

Physical Health Outcome

Physical health was considered to be the ability to perform daily activities, such as walking, household tasks, working, socializing outdoors, and the perception of not feeling limited by the physical condition of the body. The extent of physical health was assessed in the MOS-SF 36 by the distance a person was able to walk, by their ability to bend their knees, by their ability to lift heavy objects and by their general perception of health. Fatigue was a key indicator of physical health. Occurring naturally, it was a signal for the person to rest and sleep and replenish depleted energy reservoirs. Persistent fatigue was identified as a reason for a patient's inability to perform daily household tasks. It caused a substantial decline in their daily activities, and it also resulted in the patient's absence from work.

The independent blocks for the assessment of physical health contained 18 variables in four blocks for person, environment, health and illness, and symptoms (see Table 12). Person variables such as age, gender and ethnicity, high school education, college education, disability, and drug use explained 1.0% of the variance in physical health with ethnicity at 1% and disability at 4% as statistically significant predictors. Environment variables were sufficient insurance coverage and sufficient income, and explained 1.2% of the variance in physical health with income at 1% as a predictor. Length of HIV infection in years, length of an AIDS diagnosis in years, CD4 values, and viral load values were the indicators of disease progression, representing health and illness. Health and illness variables explained 5.8% of the variance in physical health, with years living with AIDS at 1%, viral load at 1%, and CD4 count at 4% as significant predictors. However, the number of participants dropped significantly due to missing data

(N=83); and therefore, the health/illness concept block was excluded from the final analysis. Symptoms, such as fatigue, depression, SOB, diarrhea and lipodystrophy accounted for 37% of the variance in physical health. The significant predictors were fatigue at 4%, depression at 5%, and SOB at 1%.

Table 12. Four Separate Multiple Regression Models Each Predicting Physical Health

	N	R^2	sr^2	df	F	p
Model 1. Person	316	.010		6,333	5.10	<.001
Age			0.00			
Gender			0.00			
Ethnicity			0.01			
High School Graduate			0.00			
College Graduate			0.00			
Disability			0.04			
Drug User			0.00			
Model 2. Environment	362	.012		2,360	2.27	0.10
Insurance			0.00			
Income			0.01			
Model 3. Health and Illness	83*	.058		4,78	1.19	0.32
Years Known HIV+			0.00			
Years Living with AIDS			0.01			
CD4 Value			0.03			
Viral Load Value			0.01			
Model 4. Symptoms	370	.325		5,364	35.05	<.001
Fatigue			0.04			
Depression			0.05			
SOB			0.01			
Diarrhea			0.00			
Lipodystrophy			0.00			

*Due to missing data

The three blocks of the final hierarchical regression model encompassed: person, environment, and symptoms, in order to determine the predictors of physical health (see Table 13). The significance of a block was determined by entering it last to determine the independent contribution to the overall model, while holding all other variables constant.

For the person block age, gender, ethnicity, high school degree, college degree, disability, and drug use were entered. The person variables explained 0.5% of the variance in physical health, with disability at 3% being the only significant predictor. Environment variables such as income and sufficient insurance coverage did not explain any variance in physical health. However, the symptom variables, including fatigue, depression, SOB, diarrhea, and lipodystrophy, explained 26.4% of the variance in physical health. The significant predictors were fatigue (2%), depression (6%) and SOB (1%). Together, the three blocks explained 37.4% of the overall variance in physical health with disability, fatigue, depression and SOB as the significant predictors.

Table 13. Hierarchical Regression Model Predicting Physical Health

	N	R^2	R^2 change	B	sr^2	df	F	p
Overall	314	37.4						
Person			0.05			7,313	3.59	<.001
Age				-0.24	0.00		2.79	.961
Gender				-2.88	0.00		1.44	.230
Ethnicity				-1.47	0.00		2.52	.113
High School Graduate				1.98	0.00		0.71	.399
College Graduate				0.94	0.00		0.07	.786
Disability				-8.54	0.03		11.05	<.001
Drug User				0.29	0.00		0.01	.113
Environment			0.00			2,313		
Insurance				-3.40	0.00		1.64	.201
Income				0.25	0.00		0.00	.927
Symptoms			26.4			5,313	25.22	.001
Fatigue				-1.23	0.02		7.77	.006
Depression				-1.82	0.06		19.16	<.000
SOB				-1.53	0.01		4.54	.034
Diarrhea				0.00	0.00		0.00	.987
Lipodystrophy				0.02	0.00		0.00	.967

[a] R^2 change when the set was added last, and coefficients and significance of the predictor when the set was added last.

Mental Health Outcome

Mental health represented abilities, such as to feel related to other people, having one's own feelings under control, being able to enjoy life, and the ability to deal with the mental challenges of life. Mental health was assessed with the MOS SF-36 using questions of whether subjects were sad, were depressed, were limited in their ability to function at work, were able to participate in social settings, or were able to handle transitions reasonably well.

The independent blocks for the assessment of mental health contained 18 variables in four blocks for person, environment, health and illness, and symptoms (see Table 14). Person variables such as age, gender and ethnicity, high school education, college education, disability, and drug use explained 5.2% of the variance in mental health. The significant predictors were ethnicity (1%) and disability (1%). Environment variables, such as sufficient insurance coverage and sufficient income, explained 2.0% of the variance in mental health, but the contributions were small and did not reach significance as independent predictors. Length of HIV infection in years, length of an AIDS diagnosis in years, CD4 values, and viral load values were the indicators of disease progression, representing health and illness. Again, health and illness indicators explained 4.7% of the variance in mental health, with years living with AIDS (1%) and viral load (1%) as predictors. However, the number of participants significantly dropped due to missing data (N=83). Therefore, the health and illness block was also excluded from the final analysis. Symptoms such as fatigue, depression, SOB, diarrhea, and lipodystrophy explained 19.6% of the variance in mental health, with depression (10%) and lipodystrophy (1%) as the significant predictors.

Table 14. Four Separate Multiple Regression Models Each Predicting Mental Health

	N	R^2	sr^2	df	F	p
Model 1. Person	316	.052		7,308	2.44	<.001
Age			0.00			
Gender			0.00			
Ethnicity			0.01			
High School Graduate			0.00			
College Graduate			0.00			
Disability			0.01			
Drug User			0.00			
Model 2. Environment	363	.020		2,360	0.27	0.76
Insurance			0.00			
Income			0.00			
Model 3. Health and Illness	83*	.047		4,78	0.96	0.44
Years Known HIV+			0.00			
Years Living with AIDS			0.04			
CD4 Value			0.00			
Viral Load Value			0.01			
Model 4. Symptoms	370	.196		5,364	17.71	<.001
Fatigue			0.00			
Depression			0.10			
SOB			0.00			
Diarrhea			0.00			
Lipodystrophy			0.01			

Three blocks were entered to determine predictors of mental health including person, environment, and symptoms in the final hierarchical regression model (see Table 15). The significance of one block was determined by entering it last to determine its independent contribution to the overall model, while holding all other variables constant.

Age, gender, ethnicity, high school degree, college degree, disability, and drug use were entered for the person block. The person variables explained 4.0% of the variance in mental health. The significant predictors were gender (1%), ethnicity (1%), high school degree (1%) and disability (1%). Environment variables, such as income and sufficient insurance coverage explained 1% variance in mental health. However, none of the variables were significant independent predictors. The symptom variables (fatigue, depression, SOB, diarrhea and lipodystrophy), explained 18.0% of the variance in mental health, with depression (8%) and lipodystrophy (2%) being significant predictors. Together, the three blocks explained 23.2% of the overall variance in mental health. The significant predictors were gender, ethnicity, college degree, disability, the frequency of depressive symptoms (CES-D) and lipodystrophy.

Table 15. Hierarchical Regression Model Predicting Mental Health

	N	R^2	R^2 change	B	sr^2	df	F	p
Overall	314	.232						
Person			.04			7,313	1.93	.064
Age				0.04	0.00		0.14	.703
Gender				3.79	0.01		3.69	.056
Ethnicity				-1.36	0.01		3.32	.069
High School Graduate				3.79	0.01		4.07	.045
College Graduate				0.09	0.00		0.00	.973
Disability				-3.91	0.01		3.59	.059
Drug User				0.19	0.00		0.00	.915
Environment			.01			2,313	1.16	.313
Insurance				0.23	0.00			
Income				2.84	0.00			
Symptoms			.18			5,313	13.73	<.001
Fatigue				-0.10	0.00		0.08	.769
Depression				-1.73	0.08		26.83	<.001
SOB				-0.25	0.00		0.18	.668
Diarrhea				-.065	0.00		2.44	.119
Lipodystrophy				1.14	0.02		6.25	.013

R^2 change when the set was added last, and coefficients and significance of the predictor when the set was added last

CHAPTER FIVE

DISCUSSION

In the past, the majority of symptom research was conducted predominantly in Caucasian and Latino HIV/AIDS samples (Breitbart et al., 1998; Cunningham et al., 1998). The sample for this study consisted of two-thirds African American participants. Most of them were poor, uneducated, yet managing their lives on an outpatient basis. This unique opportunity in fatigue research needed to be considered when the findings of this study were generalized to the population. It also provided a rare opportunity to understand some of the reported symptom patterns of African Americans. Little has been published about the symptom experiences of fatigue in African-Americans.

Proposed Study Aims

The first aim was to describe the intensity of fatigue by selected person, environment, and health and illness variables. For this study, two fatigue scales (SSC-HIVrev fatigue factor score/SCSMS) and one vitality scale (MOS SF-36 vitality scale) were utilized to evaluate fatigue and vitality. They were viewed as the two endpoints of the energy continuum. Each scale proved to have valid and reliable psychometric properties. The majority of the study participants completed the SSC-HIVrev (N=368), the MOS SF-36 vitality scale (N=354), and 144 subjects completed the SCSMS for fatigue. These 144 men and women were affected enough by their fatigue and had develop self-care strategies. The vitality scale and the two fatigue scales were brief (4-

item scales), which captured the intensity, and/or duration of fatigue and vitality. The 4-item SSC-HIVrev fatigue factor score was selected to calculate the regression analyses.

However, the SSC-HIVrev fatigue factor score consisted of 4 items: fatigue, muscle aches, weakness, and painful joints. They were the four succinct phenomena taken together under one factor score - fatigue. The fatigue that was classified in the SSC-HIVrev factor might or might not have been fatigue. Muscle aches, weakness, and pain joints could have been signs of arthritis, wasting syndrome, fibromyalgia or signs of infection. The factor analysis loaded together these items as one factor. The researcher should exercise caution when generalizing statements to the public relating to fatigue. The fact of grouping together symptoms under one concept, pointed to symptom clusters, and the ways with which symptom research should be conducted in the future. In addition to being composed of conceptually different symptoms the SSC-HIVrev fatigue score had a second weakness. The patients were asked to rate their fatigue experiences on the day they completed the instrument, which left symptom experiences of the prior week altogether unreported.

The results of this investigation supported previous findings that Caucasians, Hispanics and African American women (Schuman et al, 2001) reported higher fatigue scores than African American men. However, in this study, African-American men and women, reported equal levels of fatigue and vitality scores. Did they experience fatigue differently? There has been insufficient data in ethnic symptom reporting. A study in asthmatics revealed significant ethnic differences in reporting upper and lower respiratory descriptors (Hardie, Janson, Gold, Carrieri-Kohlman, & Boushey et al., 2000). This could be true for fatigue as well, and should be considered in future research.

The findings of this study confirmed previous research, that fatigue was affected by gender differences. Caucasian and Latino women reported higher fatigue scores than men (see Appendix 8). This could be due to the fact that they are socially allowed to complain more about fatigue than men, and have a higher risk of depression in the general population due to childbearing factors and hormonal influences. Another reason could be the hormonal differences between men and women. Women are physiologically more inclined to experience fatigue than men. Considering the results of a sub-analysis in African-American men and women, there were no differences found in reporting fatigue or vitality. Culturally, that could mean that it would be more acceptable for both genders to perceive and report bothersome symptoms, including fatigue. The reporting of such symptoms in African American men contrasted the reporting of other ethnic groups. Latino and Caucasian men were more likely to endure their symptoms and protect their male image than African American men (Dugglebey, 2003).

If these ethnic and gender differences occurred across the spectrum of different symptoms, a medium fatigue score in an African-American man or a woman would be the same as a high score in a Caucasian man or a woman. Healthcare providers should be aware, if a culturally different symptom reporting occurred across symptoms. This awareness would help them understand the severity of the experienced symptom within these specific ethnic groups. This new awareness could contribute to a better understanding of their patients' needs, and possibly increase the offering of treatment options.

Age, education, housing situation and the number of children did not present significant differences in reporting fatigue. Despite previous research findings, age was

not a significant predictor. This might be due to the fact that the average age was almost 40 years, and many adults have already become accustomed to a certain lifestyle. Stressful lifestyle changes might have been less frequent in the age groups of 31-49 and 50-60 years compared to 20-30 years. Those potential changes for the 20-30 and 50-60 year old could be: graduation, employment change, childbirth, marriage, retirement, or menopause. Education, housing, and children were insignificant predictors for fatigue, most likely because the men and women were too homogenous, regardless of ethnic background.

The second aim was to explore the potential confounding of fatigue and depression through an analysis of convergent and divergent correlations and known-group differences. Fatigue and depression scores were compared by gender. It was confirmed as in previous studies, that women scored higher on fatigue and depression than their male counterparts (Cjederfjall et al., 2001). Their multi-tasking lives and their multiple roles might be the cause. Also they might be exposed to much higher levels of physical and emotional stress through the mixture of care giving, participation in the work force and self care (Antoni, 2003; Catz, Goe-Felton & McClure, 2002). Another explanation could be the earlier onset in hormonal changes (decrease in testosterone), which could contribute to an increase in fatigue and sleep disturbances (Huang et al. 2003, Mazer, 2002). While men have higher testosterone levels in the blood, a smaller change in testosterone levels in women could have a greater impact on their fatigue.

Fatigue and depression scores were compared by age category. In this sample, the mean age was 40 years, and age was categorized into two groups of < 40 years and > 40 years. No significant differences were found between age and fatigue and depression

scores. However, on the CES-D, the average score was 28. The CES-D had a set point of 16 suggesting that almost every participant was reporting depressive symptoms worthy of clinical assessment for depression. Similarly high CES-D scores were found in a study of HIV-infected drug users in Seattle where 47% of the IV drug users scored 23 or higher (Perdue, Hagan, Tiede, & Valleroy, 2003). Currently, no good explanation can be given for the higher frequency of depressive symptoms. One speculation could be, that in general, African-Americans reported higher levels of depressive symptoms as part of their cultural upbringing. Another speculation could be that one-half of the participants were already diagnosed with AIDS, and it was the reason why they reported a more depressive outlook on life.

Fatigue and depression were explored by the levels of CD4 counts. Participants were divided into three groups: < 200 CD4 count, 200-500 CD4 counts, and > 500 CD4 counts. These CD4 groups corresponded to common treatment practices in HIV care. Those with CD4 counts < 200 were typically advised to begin an antiretroviral regimen and subsequently monitored, and those > 500 were usually not recommended to begin a regimen unless they had an opportunistic infection. There was no mean score differences in either fatigue or depression among the three different groups of CD4 counts. Three questions were asked, whether people with < 200 CD4 cells would experience severe fatigue, whether people with 200-500 CD4 cells would experience moderate fatigue, and whether people with >500 CD4 cells would experience mild fatigue or none. None of the questions could be answered, most likely due to high amounts of missing data in CD4 counts and viral loads in the sample. The CD4 counts and viral loads in this study were recalled by the patients' memory and were not confirmed by a chart review: a reason why

a third of the sample had $CD4^+$ cell counts and viral loads. Another reason might be that $CD4^+$ cell counts were not related to a perceived fatigue. The explanation for this could be that the $CD4^+$ cells were a small fraction of the leukocytes and contained the lowest numbers of mitochondria, compared to other cell types. Furthermore, patients might not have been able to perceptually recognize a physical difference during the increase or decrease of the $CD4^+$ cells. The $CD4^+$ cells within the leukocytes were a smaller fraction and they did not contribute to the overall energy production of cells. The same could be true for the relationship between fatigue and viral load. After the initial acute infection with HIV, the CD4+ cells returned to a more stable level for the next 5-10 years. Even with high viral load levels and the slow destruction of the CD4+ cells, there might not be a connection between fatigue experiences and higher numbers of viral copies in the blood. The sample would need to be quite large in order to demonstrate a significant relationship between fatigue and viral load. The viral load had a large standard deviation and it had a copy range (0-3,000,000). So far, none of the studies had sufficient results in regards to viral loads to prove an existing relationship (Breitbart et al., 1998; Barroso, Carlson & Meynell, 2003).

Fatigue and depression shared as much as 41% of the common variance between the SCSMS and the SSC-HIVrev. However, the CES-D, the SCSMS and the SSC-HIVREV fatigue scales shared only 10% variance. These differences highlighted the importance of more specific instrumentation with higher number of items. The items of both concepts were within the same scales and in a very close proximity of each other. They accounted for 41% of the shared variance and both scales included a wide range of symptoms within the concepts of fatigue and depression. Further studies should be

conducted to evaluate the items of these scales. Also, it might be very difficult for the patient to distinguish somatic symptoms of depression and fatigue. While a patient perceived himself as more physically affected and classified it as fatigue, another one might suffer more from the mental effects and could classify himself as depressed. A longitudinal study of symptoms with different symptom profiles would provide better insights into the development of certain symptoms. Understanding the multidimensionality of both concepts would be of necessity to decide whether the patient was suffering primarily from fatigue or depression.

A valid argument could be made that fatigue could be the cause and the leading symptom of depression. However, chronically fatigued people might be frustrated with the limitations they would experience, such as persistent sadness, hopelessness and psychological symptoms of classic depression. Fatigued and depressed patients shared sleep disturbances and cognitive disturbances while being sleep deprived. However, significant differences do exist. For example, depression is treated with an early rising to eliminate most of the REM sleep (one major marker of depression) (McEnany, Hughes, & Lee, 1996). Most of the chronically fatigued HIV/AIDS patients had no problems waking up and rising early. However, they would need one or two extra naps throughout the day to recuperate their short periods of available energy. They would also need physical exercises to help them maintain muscle tone and increase their strength for prolonged periods of time (Smith et al., 2001).

In this one-time assessment it could be expected that patients suffering from fatigue would also rate themselves depressed because of the limiting quality of life they experience. Evidence for the dual presence of both concepts was found when analyzing

the numbers of people who completed the SCSMS fatigue and depression questionnaires. 144 subjects rated fatigue, and 151 subjects rated depression as their major symptom. The majority of 115 subjects rated both symptoms to be a major issue in their daily lives that triggered self-care activities. Symptom diaries over prolonged periods of time would be necessary to better understand and identify potential sufferers of both, fatigue and depression.

The third study question was aimed at testing the UCSF-SMM by exploring the contribution of fatigue to the physical and mental health in patients with HIV/AIDS. A prominent observation was a large number of variables correlated with fatigue. Fatigue was a central phenomenon and it was influenced by many factors. The person variables, such as age, gender, education, and disability, for example, were correlated rather weakly. That meant that people with HIV/AIDS were less influenced by those types of external fatigue factors. They might have added to the stress of being fatigued, but symptoms, such as diarrhea, SOB, lipodystrophy and depression predominantly contributed to the symptom experience. Quality of life correlated moderately with fatigue, which supported previous findings (Groopman, 1998; Moyle, 2002).

The correlation matrix was the first indicator that all variables were highly intercorrelated. They needed to be separated into conceptual blocks. The structure of the UCSF-SMM was easily applied to the theoretical assumptions that person and environment variables had direct impacts on health and illness (HIV/AIDS). Person, environment and health/illness variables together influence symptoms, such as fatigue in HIV/AIDS, and those symptoms impact quality of life. The assessment of the block variables provided a first glimpse at the blocks that had significant impact on fatigue.

The symptom block (47%) and the quality of life block (30%) were the strongest blocks. By now it was obvious that a conceptual shift was needed. The quality of life and the symptom variables shared a great amount of variance and no new insight would have been gained by trying to regress the quality of life to fatigue. The division of quality of life into a physical and mental health summary score seemed to be a logical consequence in assessing the contribution of fatigue intensity. When fatigue was entered into a separate symptom block and regressed on physical health, it accounted for 4% of 26% variance in the symptom block. The SSC-HIV fatigue intensity was a prominent symptom in physical health, however, in the same block, the CES-D depression score explained 5% of the variance in the symptom block. Fatigue and depression were also predictive of each other (r= 0.29 to 0.34 and 0.61 to 0.64 see page 96).

In the final hierarchical regression model, symptoms, such as fatigue (2%), SOB(1%), depression (6%) and the person variable disability (3%) uniquely contributed to the overall model variance. The significance of these findings was that patients suffering from long-term symptoms, such as fatigue, perceived themselves disabled.

The block-wise regression models revealed different observations when focused on mental health (see Table 12). In the person block, disability (1%) and ethnicity (1%) were predictive of (5%) of the total variance in mental health. Some demographic variables showed a small amount of variance in mental health, regardless of age, gender, education or drug use. These findings confirmed that low numbers of drug users were predictive of lower fatigue intensity scores. However, sufficient income and health insurance were not predictive of mental health scores. Despite theoretical assumptions that better healthcare coverage would be indicative of higher mental health scores, there

was not sufficient evidence for such a relationship. One reason for not being able to establish such a relationship was that all of the participants were treated at a publicly funded clinic. It provided them with a legitimate security that their healthcare needs would be met.

Years living with HIV and CD4 values were not predictive of mental health. However, the years living with AIDS (4%) and viral load (1%) were significant predictors within the health and illness block. This might reflect the advances that have been made in the treatments of HIV/AIDS. People with HIV that have not progressed to AIDS might perceive themselves to be living fairly normal lives. However, people with AIDS might have experienced the impact of an AIDS defining illness; and therefore, they could perceive themselves to be living less normal lives. In the symptom block, depression was the most significant predictor and confirmed the high CES-D scores. In people with HIV/AIDS, depression was a serious mental condition. It greatly impacted the mental health of the patient. Regardless of age, gender and ethnicity, depression would always be of great concern when caring for an HIV/AIDS patient.

The hierarchical regression models confirmed that the UCSF-SMM was an important guide of this research project. The fact that symptoms predicted quality of life, had been confirmed a number of times (Holzemer et al., 1999; 2001; Newshan, Bennett & Holman, 2002). Recently, symptom management research in cancer patients experienced a change of focus from one particular symptom, such as fatigue or pain, to an assessment of physical and psychological symptom clusters (Dodd, Miaskowski & Paul, 2001). Symptom clusters are groups of symptoms, which occur simultaneously. Pain, fatigue and insomnia are three of the most frequent symptoms. Often, sufficient

symptom control of one of them would have positive effects on the entire cluster (Newshan, Bennett & Holman, 2002). In this study, physical symptoms that occurred together included fatigue, SOB and depression. They suggest that fatigue and SOB affect the patient's ability to rest and sleep. They also caused a moderate secondary fatigue, which was dependent on the frequency and intensity of each symptom.

Lipodystrophy was identified as a predictor of mental health. The wasting of the fat deposits in the facial areas and their increase in the abdominal fat deposits, make the HIV-infection much more apparent. These body changes should be considered seriously because of their psychological aspects on the mental health in patients with HIV/AIDS. They would cause a substantial decrease in social activities, an increase of fear of being stigmatized, and might also force the patient to emotionally withdraw from society (Martinez, Garcia-Viejo, Blanch, & Gatell, 2001).

These clusters of symptoms, that patients experienced, might be real symptoms of a present infection or a developing neoplasm. However, these clusters occurred as side effects in patients with HIV/AIDS taking HAART, which also had devastating effects on the multiple organ systems (Doerfler, 2002). The differentiation between a symptom and a side effect was unimportant in the assessment of symptoms. However, it would be of great importance to the practitioners to lessen their patients' symptom burdens by administering the most appropriate interventions. Whether a patient experienced treatable fatigue due to a viral infection or a fatigue due to the intoxicating effects of HAART, the fatigue treatments would become of great importance for the HIV/AIDS symptom management.

Limitations

Secondary analyses have advantages and disadvantages. While it provided the investigator with instantaneous access to data and the concepts of interest, there were a number of limitations that needed to be considered. The investigator had no influence on the selection of the instruments utilized in the study. There was no multi-dimensional assessment tool for fatigue as in Piper or Lee's fatigue scales (Lee et al., 1991; Piper et al., 1998). This would have added to the strength of the findings, and perhaps, supported the importance of fatigue as a critical symptom. By utilizing shorter assessment tools, the multiple dimensions of fatigue were lost, and the severity and frequency provided a less complete assessment of the symptom experience in patients with fatigue.

The second limitation was the self-report values of the CD4+ cell counts and the viral loads. In this situation, a chart review would have been more reliable, and would have provided more accurate data to assess the relationships. However, the data set was closed at the time of the data analysis, and retrospectively, there was no possibility to access additional information on the physiological values.

Unfortunately another issue arose. The study did not assess sleep disturbances or daytime sleepiness as differentiated from fatigue. There was only one insomnia item in the SSC-HIVrev instrument. From a measurement point of view, it was deemed not stable enough to be included in the analysis.

The final concerns in the community sample were the literacy levels of the participants and their understanding of the symptom terminology used in the surveys (Kalichman, Katz, Ramachandran, 1999). It would have been of great interest to assess the overall literacy levels, and to examine the number of the terms used in the survey, in a

sample with lower levels of education. During the data collection, the researchers directly provided information to the participants. Many of them might have tried to hide their lack of understanding, and instead, only completed the terms, which were culturally and intellectually familiar to them. In the study of symptom descriptors between Caucasian and African-American asthmatics, it was discovered that the African-Americans used different terminology to describe their symptoms than the Caucasians and the Latinos (Hardie et al. 2000). More research would be necessary to understand the cultural differences between the different ethnic groups and the symptom descriptors.

Implications for Research

In the future, the research of fatigue should expand to a cluster-oriented approach. The more in-depth assessment of simultaneously occurring symptoms, such as depression, SOB, lipodystrophy and fatigue, should become the focus of future studies. There was insufficient data regarding the interplay of physical and mental symptoms. In the research literature, fatigue, SOB and insomnia, individually, have had potential contributions to the development of psychological symptoms. And the interplay between them would have to be investigated further in future studies. They could also trigger the use of path analysis or causal models (structural equation models), which would be able to handle a much greater number of relationships at once.

Fatigue research should focus on the development of a biomarker, which would be a powerful tool to validate the subjective symptom experiences. It would also validate the non-pharmacological interventions for fatigue that have been used to treat fatigue in people with HIV/AIDS. One possibility would be to develop a biomarker to investigate

the function of mitochondria in different types of cells in an HIV-exposed tissue. The differences that could be observed might lead to genetic and proteomic differences and might be related to their subjective fatigue ratings. The results of this study ascertained that fatigue did not occur in isolation, but instead affected a number of systems simultaneously.

Implications for Nursing Practice

Fatigue in HIV/AIDS patients was a difficult symptom because of its multi-causal nature. Exercise, reduction in caffeine intake or a brief nap in the afternoon could be helpful strategies in managing physical fatigue. An early arousal from sleep, memory games and other mind stimulating activities might be good strategies for mental fatigue. When fatigue experiences were interpreted as tiredness, it might have taken a long time to recognize that chronic fatigue was outside the norm of daily tiredness. For nurses, the standard assessment of pain had become the fifth vital sign in their daily routines. The same attention in a nursing assessment should be paid to the assessment of fatigue and energy pattern (Gordon et al., 2002).

Focusing on the issue of fatigue and energy patterns were important to the participants of a study with HIV/AIDS (Voss, 2001) The participants no longer discussed with their healthcare provider's possible treatments of fatigue, because of their providers inability to make any new treatment recommendations. Better symptom documentation with specific diaries could be a way to improve the communications between patients and providers. It would provide the patients with a record of their different fatigue dimensions, their durations, and the intensity of fatigue experiences over a specific period of time. Thus, patients and their healthcare providers would have an opportunity to

evaluate certain fatigue patterns that would occur. Furthermore, diaries could be useful tools to assess the side effects caused by HAART. Diaries also could be useful as an early warning sign of drug toxicity and be of help in the efforts of the healthcare providers to improve a patient's regimen.

For patients, a symptom diary could be a guide in their self-care management strategies. They could review and evaluate the effects of interventions, such as exercise, decreased caffeine intake (Dreher, 2003), change of sleep patterns or acupuncture. This review might be an empowering experience, and could prevent the development of depressive symptoms and social isolation. Being in control and experiencing a successful symptom management can be an empowering experience for a person living with HIV/AIDS.

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APPENDICES

APPENDIX 1 Consent Form

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

CONSENT TO BE A RESEARCH SUBJECT

Symptom Management in Persons with HIV Disease

PURPOSE AND BACKGROUND

William L. Holzemer, RN, PHD, Professor at the UCSF School of Nursing is conducting a study to examine how HIV-positive persons manage symptoms related to HIV disease and treatment.

PROCEDURES

If I agree to be in the study, the following will occur:

1. I will be asked to answer questions about myself, and my physical and psychological symptoms and how I mange them.

2. This will take place at the Thomas Street Clinic and will take about 60 minutes (enrollment, completion of informed consent and assessment survey).

3. I will be asked to complete the questionnaires at the time of my enrollment in the study.

RISKS/DISCOMFORTS

1. Risks or discomfort in participating in this study may be the potential loss of privacy or confidentiality.

There may be some discomfort from being asked to think about my current problem related to my HIV diagnosis.

I may become tired while completing the questionnaire.

My answers will be kept as confidential as possible. I am under no pressure from my doctor or nurse to participate. My care will not change as a result of my responses to the survey. Study records will be kept confidential. No individual identities will be used in any reports or publication resulting from this study. The surveys will be coded and when completed will then be kept in a confidential file. Only the study investigators will have access to them. After the study has been completed all data will be destroyed.

BENEFITS

There may be no direct benefits to me for participating in this study, though I may be encouraged to sort through my own ideas of what would help me. It is hoped the information gained from this study will contribute to the development of knowledge of nursing practices needed by patients such as myself.

ALTERNATIVES

I am free to refuse to participate or to withdraw from this research at any time without jeopardizing my care.

COSTS

There will be no costs to me as a result of taking part in this study.

REIMBURSEMENT

I will receive reimbursement of a $ 10 incentive after I complete the questionnaires.

H.QUESTIONS

This study has been explained to me by Dr. Holzemer, or by his research assistant. If I have further questions about this study, I should first talk to the investigator. If for some reason I do not wish to do this, I may contact the Committee of Human Research, which is concerned with protection of volunteers in research projects. I may reach the Committee office between 8 AM and 5 PM, Monday through Friday, by calling (415) 476-1814 collect or by writing to the Committee on Human Research at Laurel Heights Campus, Suite 315, University of California, San Francisco, CA 94143.

I. CONSENT

I have been given a copy of this consent form to keep.

PARTICIPATION IN THIS RESEARCH IS VOLUNTARY. I am free to decline to be in this study, or to withdraw from it at any point. My decision as to whether or not to participate in this study will have no influence on my present or future care at the Thomas Street Clinic.

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Date	Subject's Signature
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Date	Person Obtaining Consent

Appendix 2. Fatigue-specific Measures

Authors	Purpose	Reliability	Validity	Utility
Revised Piper Fatigue Scale Piper, B. F., Dibble, S. L., Dodd, M. J., Weiss, M. C., Slaughter, R. E., & Pauls, S. M. (1998). The Revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. Oncology Nursing Forum, 25(4), 677-717.	To measure 4 dimensions of fatigue: behavioral/ severity (6 items), affective (5 items), sensory (5 items), cognitive/mood (6 items)	Cronbach's Alpha for entire scale 0.97	Content: Literature review and review by a 11-member national fatigue expert panel Construct: Principal component analysis Discriminant: Sensitivity testing Concurrent: Total fatigue score and subscale scores correlate with each other, with the POMS and the Fatigue Symptom Checklist scale score.	Women with breast cancer
Visual Analog Scale – Fatigue Lee, K. A., Hicks, G., & Nono-Murcia, G. (1991). Validity and reliability of a scale to assess fatigue. Psychiatric Research, 36, 291-298.	Energy (5 items) Fatigue (13 items) Morning/ Evening	Cronbach's alpha Energy (0.94/0.96) Fatigue (0.95/0.96)	Content: Descriptors from the literature & content analysis of descriptors use by patients Construct: Principal component analysis Discriminant: Sensitivity testing Concurrent: Correlates with Stanford Sleepiness Scale and POMS fatigue and vigor subscales	Healthy males and females, patients with sleep disorders
Schwarzt-Cancer Fatigue Scale Schwartz, A. L. (1998). The Schwarzt Cancer Fatigue Scale: testing reliability and validity. Oncology Nursing Forum, 25(4), 711-717	4 dimensions of fatigue: physical, emotional cognitive, temporal	Cronbach's alpha for entire scale 0.96	Content: Focused groups (healthy and cancer patients) were interviewed for selection of words to describe fatigue. Oncology nurses cross-validated the word list. All words that reached 100% of agreement were used in the pilot testing Construct: exploratory factor analysis	Physically active patients with cancer and cancer survivors

Appendix 3. Symptom Checklists (HIV-specific/nonspecific measures)				
Author	**Purpose**	**Reliability**	**Validity**	**Utility**
Adapted Symptom Distress Scale-2 Rhodes, V. A., McDaniel, R. W., Sims Homan, S., Johnson, M., & Madsen, R. (2000). An instrument to measure symptom experience: symptom occurrence and symptom distress. Cancer Nursing, 23(1), 49-54.	Symptom experience, symptom occurrence, and symptom distress of 14 symptoms with 31 items in six categories: gastrointestinal, fatigue, bowel elimination, breathing, coughing, concentration, lacrimation, changes in body temperature, appearance, and restlessness	Cronbach's alpha for symptom experience was 0.91, for symptom occurrence 0.90, and for symptom distress 0.76.	Content: Focused groups with medical-surgical and oncological patients resulted in a list of 31 items. Construct: Principal component analysis Discriminant: Sensitivity testing Concurrent: correlates positive with the Piper Fatigue Scale, the Symptoms of Stress Inventory, and the Psychosocial Adjustment to Illness Scale.	Men and women with different types of cancer and HIV
Revised Sign and Symptom Checklist- HIV Holzemer, W. L., Hudson, A., Kirksey, K. M., Hamilton, M. J. & Bakken. S (2001). The Revised Sign & Symptom Checklist for HIV SSC-HIVRev). Journal of the Association of Nurses in AIDS Care, Journal of the Association of Nurses in AIDS Care, 12(5), 60-70.	Symptom occurrence, distress of: physical (62 items) , psychological (4 items), and gynecological (8 items) symptoms	Cronbach's alpha 0.90 for the entire checklist	Content: A nurse and nurse practitioners working in direct HIV patient care met to create eight symptom items that were added to be completed only by women. Items were selected based upon a literature review and the expert clinicians' recommendations Construct: Principal component analysis Discriminant: Sensitivity testing Concurrent: Measured in a step-wise multiple regression with 11 Health Status Scores as dependent variables and eight SSC-HIVREV factor scores as predictors.	HIV infected men and women.

Author	Purpose	Reliability	Validity	Utility
Memorial Symptom Assessment Scale Short Form (MSAS-SF) Chang, V., Hwang, S. S., Feureman, M., Kasimis, B. S., & Thaler, H. (1999). Journal of Symptoms and Pain Management, 18(S20), 1162-1172.	Symptom severity, frequency, and distress of 32 symptoms.	Cronbach's alpha Was 0.80 for the general distress index, 0.82 for the physical symptom distress, 0.76 for the psychological symptom distress, and 0.87 for the total symptom distress sale. Test-retest for 1-day ranged from 0.86 to 0.94 and for the 1-week from 0.40 to 0.84.	Content: Clinical experience, literature review and content analysis. Construct: Exploratory factor analysis Discriminant: Sensitivity testing Criterion: The number of symptoms and the summary score of the FACT-G (Functional Assessment of Cancer Therapy-General instrument) correlated closely, and the MSAS-SF parameters correlated significantly with the Karnofsky Performance Score (KPS). Convergent: MSAS-SF subscale-scores showed a sharp boundary between patients with and without metastatic disease. All MSAS-SF subscale-scores differed significantly between different KPS categories. Concurrent: The summary scales of the FACT-G and the subscales of the MSAS-SF correlated significantly to each other.	Men and women with different types of cancer, and HIV

Appendix 4. Depression Measures				
Authors	**Purpose**	**Reliability**	**Validity**	**Utility**
Beck Depression Inventor (BDI) Beck, A. T., Ward, C. H., Mendelson, M. et al. (1961). An inventory for measuring depression. Archives of General Psychiatry, 4, 561-571.	To rate intensity of 21 symptoms of depression	Cronbach's alpha and Spearman-Brown ranged from 0.76 to 0.95.	Content: clinical observations of depressed patients Concurrent: BDI correlates significantly with the Hamilton Psychiatric Rating Scale for Depression, and the Zung Self-reported Depression Scale. Discriminant: Differentiates between normal and psychiatric patients. Construct: BDI is inversely related to altered REM sleep, is positively related to suicidal behaviors, and quantities of alcohol consumption. Principal component analysis resulted in 2 to seven factors	Suicide attempters, alcoholics, HIV, depressed patients, heroin addicts, male cardiac patients, married adults, high school students, healthy adults, elderly, adolescents, institutionalized elderly, and non-institutionalized elderly.

The Center for Epidemiologic Studies Depression Scale (CES-D) Radloff, S. F. (1977). The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement, 1, 385-401.	To rate 20 symptoms of depression in the general population	Cronbach's alpha for the entire scale ranged from 0.84 to 0.90.	Content: Items were selected from a pool of previously validated depression scales, clinical literature and factor analytic studies. Discriminant: CES-D scores discriminant well between inpatient and general population samples. Concurrent: CES-D correlates well with the Lubin, Bradburn, Negative Affect and Bradburn Balance, and the Cantril Ladder instruments. Construct: Principal component analysis Disriminant : Sensitivity testing	Younger and older adults, clinical depressed, HIV, chronically ill , men and women

Appendix 5. Quality of Life Measures (HIV-specific/non-specific)				
Authors	**Purpose**	**Reliability**	**Validity**	**Utility**
Quality of Life Index (QOL-I) Spitzer, W.O., Dobson, A. J., Hall, J. et al. (1981). Measuring quality of life of cancer patients: a concise QL-Index for the use by phy- sicians. Journal of Chronic Diseases, 34, 585-597.	General well being of people with terminal illnesses in five dimensions: activity level, activity of daily living, health, support, outlook each 3 items.	Cronbach's alpha is 0.78 Spearman rho correlation ranged from 0.21to 0.71.	Content: Instrument review by patients, physicians, healthy people, and researchers to review and judge the instrument. Construct: Scale and items correlated well with each other Discriminant: Sensitivity testing Concurrent: Correlated positively with the Karnofsky Performance Status Scale, moderately with the Barthel Index, the Breast Cancer Questionnaire, and with the Functional Independence measure.	Men and women with cancer, heart failure, frail elderly, HIV, chronically ill.

Authors	Purpose	Reliability	Validity	Utility
MOS-SF-20 Stewart, A. L., Hays, R. D., Ware, J. E. Jr., (1988). The MOS Short-Form General Health Survey: reliability and validity in a patient population. Medical Care, 26, 724-735.	General health status with six dimensions: Physical (6 items), role (2 items), and social functioning (1 item), mental health (5 items), health perceptions (5 items), and pain (1 item)	Cronbach's alpha For the subscales range from 0.81 to 0.88	Content: Eighteen items were adapted from the longer RAND Health Insurance Experiment Convergent/discriminant: In a multitrait analysis the patterns of correlation's indicated that physical and mental functioning scales correlated highly. Predictive: Correlations between health measures and age, sex, education, income, and race were consistent with results of using longer form measures. Discriminant: Sensitivity testing Concurrent: COOP (Dartmouth Primary Care Cooperative Information Project Chart and SF-20 scores predicted future health status in the elderly.	Men and women with different physical and mental, acute and chronic illnesses, and healthy people.

Authors	Purpose	Reliability	Validity	Utility
MOS-HIV Wu, A. W., Revicki, D. A., Jacobson, D, Malitz, F. E. (1997) Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). Quality of Life Research, 6(6),481-93	Quality of Life Measure with 11 dimensions: general health perceptions (5 items),pain, (2 items, physical functioning ((6 items), role functioning (2 items), social functioning (1 item), mental health (5 items), energy (4 items), health distress (4 items), cognitive functioning (4 items), quality of life (1 item), health transition (1 item)	Cronbach's alpha is 0.79 for the entire instrument. For the subscales range between 0.79 to 0.89.	Content: Literature review and clinical experts, 16 of the 20 items from the MOS SF-20 were taken and three additional scales were identified from the MOS. These scales included energy/fatigue (5 items), cognitive functioning (6 items), and health distress (6 items). Single items were selected: quality of life, health transition. Convergent/discriminant: Each multi-item scale was examined by determining if each item correlated more highly with other items in its own scale than with other scale scores and if each scales internal consistency score exceeded that score's correlation with other scale scores. Construct: Confirmatory factor analysis Discriminant: Sensitivity testing Concurrent: Scale scores of the MOS-HIV Short-form correlate with two other measures of health related problems and to an ACTG HIV related symptom checklist	Men and women with HIV disease.

MOS-SF-36 Ware, J. E., Sherbourne, C. D. (1992). The MOS 36-item Short Form Health Survey (SF-36). I. Conceptual framework and item selection. Medical Care, 30, 473-483.	General health status with 8 dimensions: Physical functioning (10 items), role limitations due to physical health problems (4 items), role problems due to emotional problems (3 items), social functioning (2 items), vitality (4 items, and general health perceptions 5 items, bodily pain (2 items).	Cronbach's alpha for physical functioning : 0.88 to 0.93; for role limitations (physical) : 0.84 to 0.96; for pain: 0.80 to 0.90, for mental health : 0.82 to 0.95; for role limitations (emotional): 0.80 to 0.96.; for vitality: 0.85 to 0.96; for general health perception: 0.78 to 0.95, and for social functioning: 0.68 to 0.85.	Content: Comprehensive analysis of item responses with 3, 445 patients with chronic medical or psychiatric conditions drawn from the MOS study. Item analyses confirmed the assignment of the items to the eight scales. Criterion: Comparing sale scores to ability to work, symptoms, utilization of care, and to the range of criteria for the mental health scale. Each comparison suggests significant and consistent associations with the validation criteria. Convergent/discriminant: Comparing scores for patients with varying levels of physical and mental conditions discriminated between types and levels of disease, and the scale scores discriminated between a physical diseases alone from those with a mental and physical illness. Discriminant: sensitivity testing Construct: principal component analysis Concurrent: SF-36 correlated positively with the SIP (Sickness Impact Profile), and the Quality of Well-Being Scale.	Norms are present: for 7 different age groups for the general US population, 13 different medical conditions, and for socioeconomic and the presence of chronic conditions in Great Britain.

Appendix 6. Reliability Estimates for the MOS SF-36 Subscales

Measure	N	Mean	SD	Range	# Items	Total α	♂ α	♀ α
MOS-SF HIV								
Physical Functioning	353	54.75	27.21	0-100	10	0.89	0.89	0.88
Role Functioning	366	41.64	40.43	0-100	4	0.84	0.83	0.84
Emotional Functioning	360	58.64	27.97	0-100	3	0.80	0.78	0.83
Bodily Pain	368	50.53	22.57	0-100	2	0.86	0.82	0.88
General Health	358	51.98	22.62	0-100	5	0.69	0.71	0.57
Vitality	354	61.68	27.04	0-100	4	0.69	0.71	0.64
Social Functioning	367	39.73	41.23	0-100	2	0.58	0.67	0.40
Mental Health	355	57.53	21.86	0-100	5	0.73	0.74	0.70

Appendix 7. Correlation Matrix of all Model Variables for the Multiple Regression Predicting Fatigue

Variables	**Fatigue**	**Gender**	**Age**	**High School**	**College**	**Income**	**Race**	**Disabled**	**Drug Use**	**Insurance**
Fatigue	1.00									
Gender	-0.11*	1.00								
Age	0.01	0.04	1.00							
High School	-0.07	0.10	0.12	1.00						
College	-0.02	-0.07	0.08	0.29*	1.00					
Income	0.17**	0.08	-0.09	-0.05	-0.03	1.00				
Race	0.13*	-0.01	-0.06	0.15*	0.20**	0.11*	1.00			
Disabled	0.16**	-0.02	-0.02	0.08	0.11*	0.08	0.07	1.00		
Drug Use	0.13**	0.06	0.07	-0.10	-0.02	0.03	0.11*	0.13*	1.000	
Insurance	0.05	0.05	0.05	0.07	-0.02	0.44**	0.03	-0.17**	-0.10	1.000
Depression	0.33**	-0.12**	-0.12*	0.04	0.04	0.09	0.04	0.05	0.08	-0.00
SOB	0.62**	-0.13**	-0.13	-0.12*	-0.04	0.12*	0.10	0.05	0.13	-0.01
Diarrhea	0.59**	-0.11**	-0.11*	-0.03	0.04	0.12*	0.16*	0.07	0.10	0.03
Lipodystrophy	0.48**	-0.15**	-0.15**	-0.11*	0.02	0.01	0.11*	0.15**	0.04	-0.02
Physical Funct.	-0.36**	0.01	-0.15**	0.03	-0.10	-0.05	-0.08	-0.22**	-0.18**	0.00
Role-Physical	-0.40**	-0.00	-0.16**	0.11*	0.02	-0.10	-0.06	-0.23	-0.12*	-0.05
General Health	-0.44**	0.02	-0.11**	0.06	0.05	-0.16**	-0.11*	-0.16**	-0.07	-0.08
Social Funct.	-0.42**	0.07	-0.07	-0.03	-0.01	-0.6	-0.11*	-0.16**	-0.07	-0.01
Role Emotional	-0.32**	0.00	-0.05	0.08	0.02	-0.06	-0.11*	-0.14**	-0.15*	-0.03
Mental Health	-0.39**	0.08	0.02	0.03	0.03	-0.13*	-0.14**	-0.65	-0.14*	0.01

Health Transit.	0.24**	-0.05	0.03	-0.02	0.06	0.18**	0.08	-0.01	0.15*	0.10
HIV Duration	0.04	0.14**	0.08	0.10	0.13*	0.17**	0.11*	0.20**	0.14*	0.15**
AIDS Duration	0.04	0.15	0.119	0.07	0.10	-0.10	0.03	0.11	0.06	0.12
CD4 Value	-0.10	-0.15	-0.08	0.09	0.09	0.00	0.09	-0.05	0.00	0.22**
Viral Load	0.03	0.07	-0.13	-0.20*	0.13	0.18*	0.03	-0.12	-0.03	0.14

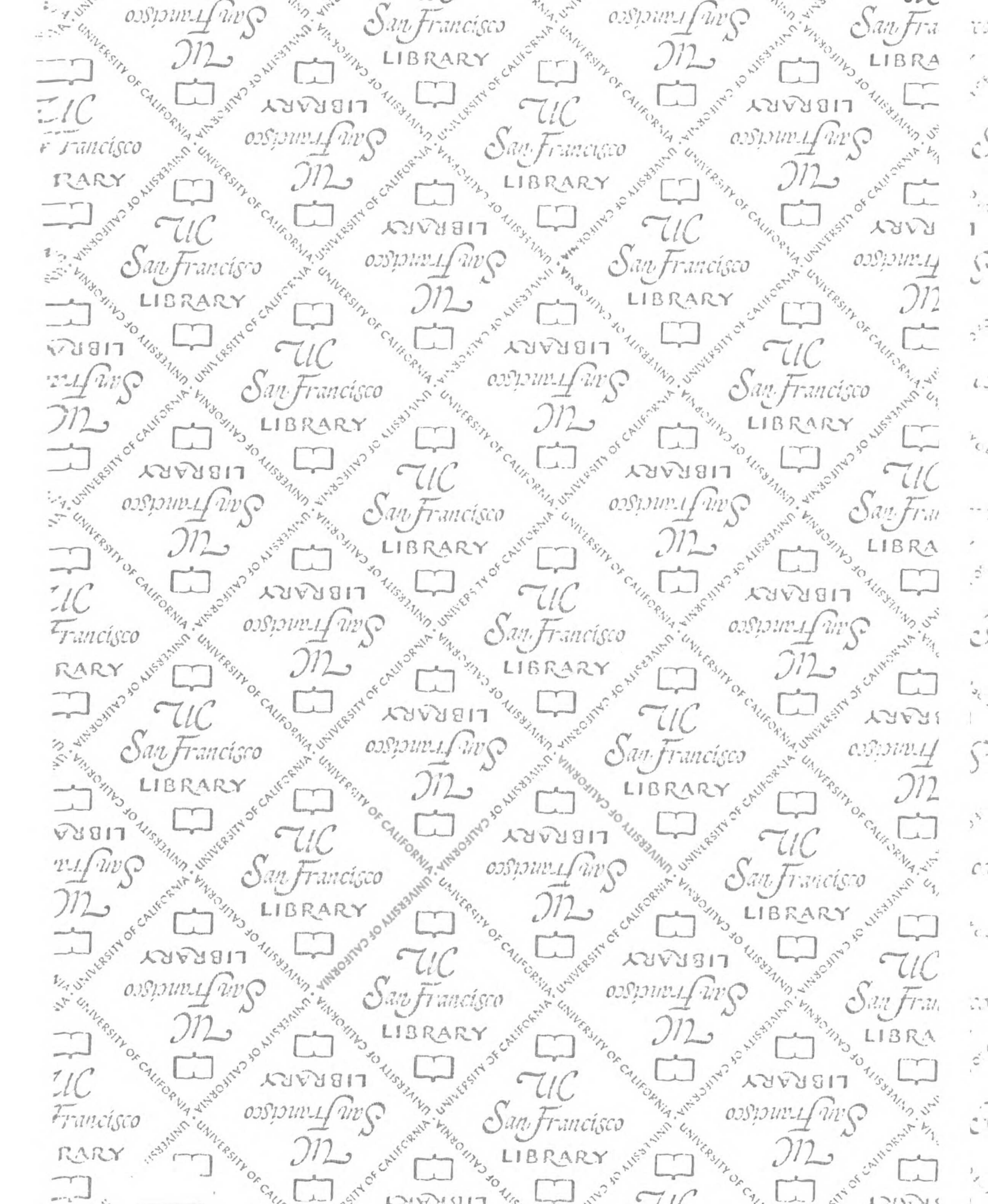
Variables	**Depression**	**SOB**	**Diarrhea**	**Lipodyst.**	**PF**	**RF**	**GH**	**SF**	**RE**
Depression	1.00								
SOB	0.31**	1.00							
Diarrhea	0.33**	0.65**	1.00						
Lipodystrophy	0.26**	0.51**	0.47**	1.00					
Physical Funct.	-0.17**	-0.34**	-0.29**	-0.24**	1.00				
Role-Physical	-0.20**	-0.32**	-0.26**	-0.17**	0.47**	1.00			
General Health	-0.32**	-0.42**	-0.34**	-0.28**	0.42**	0.48**	1.00		
Social Funct.	-0.48**	-0.34**	-0.34**	-0.29**	0.41**	0.46**	0.52**	1.00	
Role-Emotional	-0.27**	-0.26**	-0.27**	-0.10	0.37**	0.67**	0.39**	0.43	1.00
Mental Health	-0.50**	-0.37**	-0.37**	-0.30**	0.25**	0.34**	0.49**	0.56**	0.46**
Health Transit.	0.23**	-0.23**	0.16**	0.20**	-0.25**	-0.34**	-0.44**	-0.33**	-0.33**
HIV Duration	-0.03	0.06	0.08	0.08	-0.18**	-0.14**	0.10	-0.10	-0.13*
AIDS Duration	-0.03	0.02	0.02	0.10	0.09	0.06	-0.11	-0.07	0.03
CD4 Value	-0.14	-0.09	-0.14	-0.06	0.02	-0.07	0.11	0.10	0.01
Viral Load	-0.20*	0.10	0.18	-0.04	-0.09	-0.13	0.08	-0.02	-0.16

Variables	MH	HT	HIV Duration	AIDS Duration	CD4 Value	Viral Load
Mental Health	1.00					
Health Transit.	-0.32**	1.00				
HIV Duration	0.05	0.03	1.00			
AIDS Duration	-0.04	0.02	0.64**	1.00		
CD4Value	0.07	0.04	-0.02	0.12	1.00	
Viral Load	-0.00	0.16	0.06	-0.03	-0.21*	1.00

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Appendix 7 T-Test Results for Vitality and Fatigue Scores between Gender of Different Ethnicity

	MOS SF-36 Vitality				SSC-HIV Fatigue				SCSMS Fatigue			
African-American	M	SD	t	p	M	SD	t	p	M	SD	t	p
Male	55.89	21.08	-1.28	0.20	5.06	3.48	1.65	0.09	20.54	10.29	0.32	0.74
Female	52.24	22.71			5.81	3.49			21.25	10.32		
Caucasian												
Male	41.17	25.16	-0.06	0.94	6.20	3.68	0.30	0.76	21.40	9.31	-0.99	0.33
Female	44.33	27.63			7.20	3.87			27.33	10.14		
Latino												
Male	46.48	21.71	-0.06	0.94	7.00	3.55	0.30	0.76	25.09	10.04	0.99	0.33
Female	45.83	17.72			7.50	4.32			19.75	5.37		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