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HEALTH PROMOTION AND QUALITY OF LIFE IN HIV-1 INFECTED INDIVIDUALS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

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ABSTRACT

Stress is postulated to exacerbate the deteriorating effects of human immunodeficiency virus (HIV-1) on health outcomes of infected individuals. There are an estimated 1 to 2 million people in the United States infected with HIV-1 who face the challenges of their seropositive status. Research has shown that aerobic exercise enhances overall health status and psychological well being. Given that aerobic exercise may be beneficial in reducing stress state and improving quality of life in HIV-1 infected individuals, this study examined the effect of a 12-week aerobic exercise protocol on stress state and quality of life in HIV-1 infected individuals, assessed by salivary cortisol and the MOS-HIV questionnaire, respectively.

Subjects were selected through convenience sampling in conjunction with a parent study and randomly assigned to either the experimental or the control group. Non-parametric Mann Whitney U analyses compared the completers of the exercise protocol (n = 18) versus those who did not complete the protocol (n = 5) on age, CD4 and CD8 absolute counts and percentages; there were no significant differences between these groups.

Non-parametric Mann Whitney U analyses were used to assess for possible differences between those completing the exercise protocol (n = 6) and the control group
(n = 12) on age, CD4 and CD8 absolute counts and percentages, and pretest, posttest, and change scores of the MOS-HIV. No significant group differences emerged. An unbalanced repeated measures ANCOVA assessed for group differences in cortisol levels, and a significant group by week interaction was found (p = .007), indicating that there were differences in cortisol level between the exercise versus control group depending on the week the measurement was taken.

Several rationales may explain the absence of group differences. Possible benefits of the exercise intervention may not have been reflected in the MOS-HIV. The effect of the HIV-1 virus on HPA axis function and significant events experienced by individual subjects may explain differences between the exercise and control groups related to the timing of cortisol measurements. In conclusion, the impact of aerobic exercise on stress state and quality of life in HIV-1 infected individuals merits further study.
Dedication

To my mother and father ...

who gave me life and taught me about it.
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CHAPTER 1
INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) has emerged as the deadliest pandemic of the 20th Century. Since first reported over 15 years ago, the human immunodeficiency virus (HIV-1) has been identified as a primary cause of death among young adults in the United States (Hardy, 1996). The Centers for Disease Control (CDC) (1995) estimated that approximately 1.5 million people are infected with HIV-1 in the United States. Internationally, AIDS continues to have a detrimental impact on the world health care system (Gourevitch, 1996; Quinn, 1996). Quinn (1996) reported that an estimated 24 million adults and 1.5 million children have been infected with HIV-1 worldwide and that 10,000 new infections occur each day.

The HIV pandemic has had a damaging and disproportionate effect on Blacks and Hispanics (CDC, 1993, 1994; Gourevitch, 1996). Over the past several years, 51.4% of all AIDS cases reported in the United States have been among Blacks and Hispanics, which make up only 12% and 6% of the population, respectively (Gourevitch, 1996). Gourevitch (1996) reported that the incidence rates of AIDS among Black and Hispanic women were 17 and 7 times higher than among White females, respectively, and that the incidence rates among Black and Hispanic males were 5 and 3 times higher.
than that of White males. Since its emergence in the early 1980s, HIV has become a modern day plague which has resulted in "...unprecedented personal suffering, high direct costs from medical care, reduced economic output, and substantial indirect cost to society" (Quinn, 1996, p. 105).

Over the last decade, the development of antiretroviral drug therapy and protease inhibitor drug therapy (e.g., zidovudine, didanosine, crixivan, and invirase) has markedly improved the treatment of HIV-1 infection and prophylaxis against opportunistic infections (OIs). With the discovery of life-extending drug therapies, HIV-1 infection has come to be viewed more as a chronic illness, punctuated with OIs that can greatly impact subsequent quality of life and functional well being (Copfer, Ampel, Hughes, Gregor, Dols, Coons, Colgan, & Wu, 1996; Revicki, Wu, & Murray, 1995). In addition, the expense and rigid regimens of these drug therapies may negatively affect quality of life in HIV-1 infected individuals (Copfer et al., 1996; Holzemer & Wilson, 1995). The average cost of a year's supply of an antiretroviral drug and protease inhibitor drug (such as didanosine and crixivan) may total $2,232 to $5,400, respectively (Dr. J. Clark, personal communication, August 8, 1997). The treatment regimens required in the care of HIV patients, such as complex drug dosing schedules (which may involve multiple drugs), subsequent adverse side effects and/or interactions, and the need for long-term or even lifetime adherence to various therapies, may prove very disruptive to a HIV-1 infected patient's lifestyle (Chesney & Folkman, 1994).

The use of a health promotion strategy, such as an aerobic exercise protocol in conjunction with the new powerful drug therapies, may be beneficial in attenuating the
harmful effects of the HIV-1 virus on its human host (LaPerriere, Fletcher, Antoni, Klimas, Ironson, & Schneiderman, 1991; McCain & Zeller, 1996; Schneiderman, Antoni, Ironson, Klimas, LaPerriere, Kumar, Esterling, & Fletcher, 1994). The data collected for this study are part of a parent project entitled, "Aerobic Exercise: Effects on Physical Symptoms of HIV" (Smith, Neidig, MacVicar, Nickel, & Salsberry, 1994). This sub-study was conducted with 25 patients between September 1996 and August 1997. Preliminary results from the parent experimental study indicated that, after a 12-week exercise period, the exercise group had significantly less anger, fatigue, and depression than did randomly assigned controls experiencing their "normal" levels of activity. (Dr. Barbara Smith, personal communication, May 1, 1997). These findings may suggest that practicing an exercise regimen may provide benefits to individuals' quality of life and stress. Therefore, the purpose of this study was to examine the effect of a 12-week aerobic exercise protocol on quality of life and stress management in HIV-1 infected adults.

**Research Hypotheses**

1. The experimental group, in comparison to the control group, will have improved scores on the Medical Outcomes Survey - HIV (MOS-HIV) (Wu, Rubin, Mathews, Ware, Brysk, Hardy, Bozzette, Spector, & Richman, 1991) as a measure of quality of life over the 12-week intervention period.
2. The experimental group, in comparison to the control group, will have significantly lower salivary cortisol levels as a measure of their stress state over the 12-week intervention period.

Operational Definitions

Chronic Stress. For the purposes of this study, living with a life-threatening disease that has potential psychological, physical, spiritual, social, and financial consequences (Thompson, Nanni, & Levine, 1996); salivary cortisol is the physiological measure of chronic stress.

Maximum Aerobic Power. The highest level of total body oxygen use reached in a graded exercise test. Maximum aerobic power is also known as \( VO_2 \) maximum, oxygen consumption, oxygen uptake, and functional capacity (Lamb, 1984). Physiologically, aerobic power is defined as Maximum Aerobic Power = cardiac output (at maximum effort) \( \times \) arterial venous oxygen difference (at maximal effort). For the purposes of this study and because many relatively sedentary adults are unwilling or unable to attain their maximal physiological limits, the highest aerobic power measured will be referred to as peak rather than maximal aerobic power.

Quality of Life. An individual's perception of well being as reflected by the concepts of physical functioning, role functioning, social functioning, mental health, health perceptions, pain, energy/fatigue, cognitive function, health distress, and overall health. For the purposes of this study, quality of life was assessed by the Medical Outcomes Survey-HIV (MOS-HIV) (Wu et al., 1991).
Significance of the Study

If positive effects on health can be obtained through a non-pharmaceutical intervention (aerobic exercise), this would have clear physiological, psychological, and economic benefits in the HIV-1 population. HIV/AIDS is a disease that has a profound impact on many aspects of its victims' lives. The day-to-day ordeal of living with a positive diagnosis and the challenges of medical management of HIV-1 have led to the investigation and evaluation of non-pharmacologic interventions in the treatment of HIV-1 disease (Chesney & Folkman, 1994). Researchers continue to strive for the development of new and powerful drug therapies in the ultimate attempt to find a cure for HIV-1. The progress made in the development of new drug treatments is not without potential health and financial consequences to HIV-1 infected individuals. There may be serious side effects, as well as potentially adverse drug interactions that require monitoring. Moreover, the cost of many of these drug therapies is high, and new drugs may be limited in availability because they have yet to be approved for use by the Food & Drug Administration (FDA) (Rothman & Edgar, 1993). The ultimate approval of experimental drugs may take up to 7 years after completion and subsequent review of four drug trial stages (Grady, 1988). Although the period of development to distribution of new drugs may seem long and soporific, it is the FDA's policy to determine "definitively which drugs are effective and which drugs are safe" (Fauci, 1989, p. 116). Therefore, the use of non-pharmacologic interventions, such as exercise, may give
HIV-1 infected individuals a new sense of hope and independence in their battle against the devastating effects of HIV/AIDS.
CHAPTER 2
THEORETICAL FRAMEWORK AND REVIEW OF LITERATURE

HIV, Exercise and Psychoneuroimmunology

This chapter presents: (1) a proposed theoretical model for the relationship between HIV, exercise, and psychoneuroimmunology; (2) a review of literature related to this study; and (3) the conceptual framework that underlies this study. Initially, research on the relationship between stress and cell-mediated immunity are examined. Then, studies on the relationship between HIV-1 and physical effects of stress, quality of life, immune status, and aerobic power are discussed.

Psychoneuroimmunology (PNI) is an emerging field of study, which examines the relationship between specific psychological variables, the neuroendocrine system, and the immune system (Keller, Shiflett, Schleifer, & Bartlett, 1994). A working model for examining the effects of stress on the human organism has been proposed by Antoni, Schneiderman, Fletcher, Goldstein, Ironson, and LaPerriere (1990) (Figure 1 and reproduced in Appendix A for the reader’s convenience). This model will help to explain the relationships between the psychosocial, endocrine, and immunological variables measured in this study and may help to explain HIV-1 progression in general.
STRESS MANAGEMENT

Relaxation training/
Cognitive restructuring

Aerobic
exercise

(+) sense of control
(+) self-efficacy
(+) self-esteem

(-) anxiety, depression, social isolation

(+) parasympathetic activation
(-) sympathetic activation
(-) CRF, ACTH

(-) peripheral catecholamines and/or cortisol

(+\(\beta\)-lipotropin
(+\(\beta\)-endorphin
(+ met-enkephalin

(-) cAMP/cGMP ratio
(+ IL-I, IL-II, \(\gamma\)-IFN, MIF

(+\(\gamma\)-IFN, IL-II, LIF

IMMUNE ENHANCEMENT

(+ blastogenesis
(PHA, ConA, PWM)

(+ CD4/CD8 ratio
(+ NK cytotoxicity

DECELERATED HIV-1
DISEASE PROGRESSION?

Figure 1. Heuristic Working Model (Antoni, Schneiderman, Fletcher, Goldstein, Ironson, & LaPerriere, 1990, p. 44). A "trial & error" working model for commonly-accepted stress management effects on psycho-social, neuroendocrine/neuropeptide, and immunological endpoints relevant to human immuno-deficiency virus-type 1 (HIV-1) infection. (The symbol (+) indicates increase; (-) denotes decrease.)
Based on this framework, as well as several studies (LaPerriere, Antoni, Schneiderman, Ironson, Klimas, Caralis, & Fletcher, 1990; LaPerriere, Ironson, Antoni, Schneiderman, Klimas, & Fletcher, 1994), stressors such as bereavement or learning of one's seropositivity lead to an increase in psychological distress and a decrease in quality of life. Feelings of anxiety, depression, loneliness, and social isolation are often reported and are especially salient in people who are HIV-1 infected. An individual's perception of and response to a stressor and the ability or inability to develop a coping response to that stressor initiate a cascade of events which leads to the activation of the neuroendocrine system, specifically, the hypothalamic-pituitary adrenocortical system (HPAC) and sympathoadrenomedullary system (SAM). Activation of the HPAC system signals the release of the corticotropin releasing factor (CRF) and adrenocorticotropin hormone (ACTH) and results in the secretion of cortisol. Autonomic nervous system activation initiates the SAM system to release the catecholamines norepinephrine (NE) and epinephrine (E). The HPAC and SAM systems are vital in preparing an organism for a confrontation to a stressor. The subsequent increase in catecholamines and cortisol has been linked to a decrease in immune function, which is reflected by a decrease in natural killer (NK) cell activity, impaired responsiveness of lymphocytes to concanavalin A (Con A) stimulation, and a decrease in production of the lymphokine interleukin-1 (IL-1) (a protein that assists in the production of T-helper cells) (Antoni et al., 1990; Kennedy, Kiecolt-Glaser, & Glaser, 1988).

Antoni et al. (1990) suggested that the proposed model may be viewed as a "speculative heuristic schematic" or working model for several reasons. First, the
observed neuroendocrine changes were only a small portion of the other hormonal changes that occur during a response to a stressor which are known to cause decrements in immune function (e.g., an increase in the production of prostaglandin and somatostatin, which are released in the event of tissue inflammation and result in damage to surrounding tissues). In addition, the proposed model does not present the bidirectional loops among and within the sequence of events leading to acceleration of the HIV-1 disease (Antoni et al., 1990). The model fails to address an individual's ability to adjust and adapt to a stressor (Antoni et al., 1990). Finally, the model does not take into account the negative behavioral responses that may occur as a result to a stressor such as sleep loss, substance abuse, and dietary changes. These other behavioral responses are also known to affect immune function (Antoni et al., 1990; Kiecolt-Glaser & Glaser, 1988). Despite the limitations of the model, it may be viewed as a beginning framework in examining the stressor-related changes relevant in the study of HIV-1 disease progression.

Physical Effects of Stress

There is growing psychoneuroimmunologic literature which substantiates the relationship between stress and changes in humoral and cell-mediated immunity (Antoni, Schneiderman, LaPerriere, Bourguignon, & Fletcher, 1992; Calabrese, Kling, & Gold, 1987; Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992; O’Leary, 1990; Schneiderman et al., 1994). The capacity of the human body to fight off foreign agents that may potentially damage tissues or organs is achieved through the process of
acquired immunity. There are two basic types of acquired immunity that occur in the body – humoral immunity (B cell immunity) and cell-mediated immunity (T cell immunity). In humoral immunity, the body develops circulating antibodies that attack a foreign agent. Cell mediated immunity is achieved through the production of T helper (CD4 cells) and T suppressor (CD8 cells) lymphocytes that participate in the destruction of foreign organisms (Guyton, 1991; Kiecolt-Glaser & Glaser, 1995).

For over a decade, the effects of psychological stressors on immunocompetence have been studied in-depth. It has been hypothesized that a stressor suppresses T-helper cell and T-suppressor cell function, leading to immunocompromise and subsequent degradation in health status (Calabrese et al., 1987). Of the 1-2 million people who are estimated to be infected with HIV-1 in the United States, the clients who choose to learn their serostatus are faced with the emotional challenge of learning whether they are seropositive or seronegative and the potential social and medical consequences that are associated with a positive diagnosis (Antoni et al., 1990; Kelly, Murphy, Bahr, Kalichman, Morgan, Stevenson, Koob, Brasfield, & Berstein, 1993). The added effects produced by a psychological stressor on humoral and cell mediated immunity may further compromise the immune system of clients with HIV/AIDS. Subsequently, it may be reasonable to suggest that stress would have a negative impact on immune function and therefore overall well being of HIV-1 infected individuals (Britton, Zarski, & Hobfoll, 1993; McCain & Cella, 1995; Nott & Vedhara, 1995; Thompson et al., 1996).

In characterizing the research that explores the area of the physical effects of stress, one must first review the historical works of Selye (1956) and Cannon (cited in
Johnson & Anderson, 1990). By examining the early work of these scientists, one can gain some understanding of the evolution of research that is the basis for the modern day studies in the area of chronic stress.

Cannon (cited in Johnson & Anderson, 1990) defined stress "...as a force acting to perturb the internal homeostatic state" (p. 218). According to Cannon, the body constantly works to maintain a constant state (homeostasis) by coordinating physiological processes (Johnson & Anderson, 1990). When an animal encounters a stressor, there is a disruption in homeostasis, leading to a massive activation of the sympathetic nervous system and resulting in a fight or flight reaction in which the animal decides instantly whether to stand and fight or to run (Johnson & Anderson, 1990). The fight or flight stage is characterized by such physiological phenomena as increased blood flow to the muscles, increased cellular metabolism, increased blood glucose concentration, increased mental activity, and increased muscle strength.

Selye (1956) is one of the 20th Century's most noted figures in the area of stress research. His work in identifying and describing the signs and symptoms of the body's complex responses to long-term stressors led to the development of the General Adaptation Syndrome (GAS). The GAS has three specific stages: (1) the alarm reaction, (2) the period of resistance, and (3) the phase of exhaustion (Johnson & Anderson, 1990). The alarm reaction is the initial response to a stressor, characterized by a shock phase and a countershock phase. During the shock phase, there is an increase in heart rate, decrease in temperature, decrease in blood pressure, and a reduction in muscle tone (Johnson & Anderson, 1990). In the countershock phase, there is the
stimulation of the anterior pituitary leading to the secretion of CRF. The production of CRF induces ACTH secretion, which is then followed by the adrenocortical secretion of cortisol, which causes the mobilization of amino acids and fats, both of which are needed for energy during times of stress in animals. If the animal cannot successfully mount a defense against a stressor, it may die (Johnson & Anderson, 1990). However, if the animal survives, the stage of resistance occurs. During this second stage, the animal is able to successfully mobilize energy reserves that allow it to survive the stressor. The final condition is the stage of exhaustion. During this stage, the animal loses the ability to adapt to the stressor and exhibits the signs found during the shock phase of the alarm reaction (increased heart rate, reduced temperature, decreased blood pressure, and loss of muscle tone) (Johnson & Anderson, 1990).

Over the last 25 years, various clinical studies have been conducted to examine the physical effects of acute and chronic stress in humans. In considering this literature, one must be clear as to what time duration is referred to by an acute or a chronic stressor. An acute stressor may last for several days up to one month; a chronic stressor is thought of as lasting for more than one month (Herbert & Cohen, 1993). For the purposes of this study, the psychological, endocrine, and immunological effects of an acute and chronic stressor will be discussed.

Bartrop, Luckhurst, Lazarus, Kiloh, and Penny (1977) were the first to study the relationship between psychological state and immunological function. The authors first studied mitogen stimulation, a procedure that has commonly been used in the study of bereaved, stressed, or depressed populations (Calabrese et al., 1987). In a classic
prospective study of bereavement in 26 men and women whose spouses were critically ill, each subject provided a blood sample at 1-3 weeks and 6 weeks after the deaths of their spouses. A control group, matched for age, sex, and race with the bereaved subjects, provided blood samples that were timed similarly to that of the experimental group. The lymphocytes from the blood of the subjects were isolated and co-cultured with mitogens, plant seed extracts known to stimulate T-lymphocyte production. Mitogens used in the study were phytohemagglutinin (PHA) and concanavalin A (Con A). In the bereaved group, T-lymphocyte proliferation in response to the PHA and Con A was reduced at 3 weeks and 6 weeks after the deaths of their spouses compared to the controls. Even with higher doses of PHA and Con A, T-lymphocyte proliferation was significantly lower at 6 weeks than at the first week, suggesting that the effect of a chronic stressor was a time dependent phenomenon. The study conducted by Bartrop et al. (1977) served as an impetus for future research exploring associations between stress, immune function, and disease.

**Stress Reduction in Non HIV-1 Infected Individuals**

The pathway that leads from stress to illness is an intricate, multifaceted process that involves not only the stressful event but also an individual’s perception of the stressor and the psychological and physiological reaction to the event (Keller et al., 1994; Schneiderman & Baum, 1992). Various studies suggest that the use of biobehavioral stress management strategies can help buffer the negative effects of stress on an individual. The patient populations that have been used in many of these studies

Over the last decade, researchers have attempted to connect psychosocial stressors with tumor development and/or the progression of chronic diseases such as cancer. Issues are being explored and evaluated, such as how the stage of one's disease can affect the way a patient copes with his or her illness and how treatments such as chemotherapy and radiation impact on a patient's life. The possibility of influencing the course of a chronic disease through stress management has become a growing area of interest. Through the use of properly designed intervention studies that randomly assign patients who have the same kind and stage of cancer to control for possible confounding conditions, researchers can better assess the effect that an intervention has on psychological, immunological, and disease changes (Kiecolt-Glaser & Glaser, 1995).

Spiegel et al. (1989) conducted a 10-year longitudinal study which evaluated the effect of weekly supportive group therapy sessions with self-hypnosis for pain management on survival time in 86 women with metastatic breast cancer. The groups were randomly assigned to a therapy group (n = 50) and control group (n = 36). The therapy group consisted of a weekly 90-minute session in which patients were encouraged to express their feelings about their illness and its impact on their lives. In addition, self-hypnosis sessions were taught for pain control. The intervention lasted for
one year, and both treatment and control groups received standard oncological care. Unfortunately, no immunological measures were obtained in this study; however, at the 10-year follow-up, the authors found that the therapy group survived on average of a 1.5 years longer than did the control group. The 10-year follow-up showed that the divergence in survival began 20 months after the intervention ended.

Similarly, Fawzy et al. (1990) evaluated the effects of a structured, short-term, psychiatric group intervention consisting of health education and stress management on psychological distress and immune cell measures. The intervention was conducted for 6 weeks with postsurgical patients with Stage I or II malignant melanoma who had not received any treatment after surgical removal of the cancer. The experimental subjects (n = 38) were involved in sessions that consisted of health education, enhancement of problem solving skills, relaxation techniques, and psychological support. Outcome measures included the Profile of Mood States (POMS) (a 65-item questionnaire measuring multiple aspects of affective state and coping style), the Dealing with Illness-Coping Inventory (a 48-item questionnaire assessing cognitive and behavioral responses made in efforts to cope with illness), NK cell activity, and T-helper cell count. At the end of 6 weeks, the researchers found that the experimental group reported higher levels of vigor, lower levels of anxiety, confusion depression and fatigue, and used active-behavioral coping methods (e.g., exercise and relaxation techniques) significantly more often than did the control group. At 6 months follow-up, the researchers reported that the experimental group had significant increases in the percentage of NK cells, an increase in NK cytotoxic activity, and a small decrease in the percentage of T-helper
cells; continued to report lower levels of psychological distress; and, used significantly more active-behavioral coping methods than did the control group.

Although the findings from these studies may reflect the immunological changes that influenced the course of the cancer, other possible explanations are feasible. The patients in the experimental groups could have been more compliant with medical treatment and had better health behaviors (e.g., diet and exercise); such behaviors could have contributed significantly to the outcome (Kiecolt-Glaser & Glaser, 1992; Spiegel et al., 1989).

The use of stress management has also been documented in such populations as older adults, undergraduate students, and medical students. Many of these studies have used various intervention strategies, including hypnosis, relaxation, and self-disclosure. Although there is diversity in the methodology and immunological measures, these studies suggest that there is a strong relationship between the effects of stress on immunity and health outcomes in various populations, and that behavioral interventions may have positive consequences on immune function and psychological health.

Several studies by Kiecolt-Glaser et al. (1985) and Kiecolt-Glaser, Glaser, Strain, Stout, Tarr, Holliday, and Speicher (1986) have explored the effects of relaxation and hypnosis on various aspects of cellular immunity in two different populations. In one study, the authors assessed the impact of relaxation and social contact with 45 older adults from four independent living facilities (Kiecolt-Glaser et al., 1985). Subjects were randomly assigned to one of three protocols: progressive relaxation training, social contact, or no intervention. Subjects in the relaxation training and social contact groups
were seen 3 times a week for one month. Outcome measures collected were NK cell activity and Herpes Simplex Virus (HSV) antibody titers. Subjects in the relaxation group had significant increases in NK cell activity and decreases in HSV antibody titers, both measures indicating an improved immune function. Similarly, Kiecolt-Glaser et al. (1986) assessed the effects of a hypnotic/relaxation protocol on T-helper cell count and NK cell activity in 34 medical students. Half of the medical students were randomly assigned to a hypnotic/relaxation group that met for 10 sessions. Blood for lymphocytes was collected at baseline and one month before examinations in mid-November; the last blood draw was on the final day of the 3-day mid-December examinations. The authors concluded that NK cell activity and T-helper percentage declined in both groups during examinations. In addition, the hypnotic/relaxation group showed wide variability in their relaxation practice, ranging from 5 to 50 times. Regressional analyses showed that more frequent practice was associated with higher T-helper cell percentages during examinations after controlling for baseline levels.

The use of self-disclosure has also been used as a stress reduction technique in certain groups. Pennebacker, Kiecolt-Glaser, and Glaser (1988) asked 50 healthy undergraduates to write about their traumatic experiences or other unrelated topics for four consecutive days. The authors hypothesized that writing about the traumatic experiences would be less stressful than a failure to disclose the experience. The writers who chose to write about their trauma reported a short-term depression; however, in the long term, they reported being happier and less depressed 6 months after the study compared to the controls. T-helper cell proliferation to Con A and PHA mitogens
improved in the trauma writers compared to that of the controls, suggesting the positive effect of confronting and expressing traumatic experiences on overall health.

Although the aforementioned studies suggest that the use of various stress management techniques may buffer the detrimental effects of stress on some immune measures and promote psychological well being, there are several issues that must be addressed. To date, much of the work in stress research has been primarily conducted in acute stress settings, and most of the studies on chronic stress have been cross-sectional in design (Herbert & Cohen, 1993). Moreover, much of the stress related research literature has been difficult to integrate because of lack of conceptual clarity as to how stress has been defined (the occurrence of a negative stressor or perception of a stressor) and an inconsistency in the collection and measurement of multiple variables (Herbert & Cohen, 1993; Kiecolt-Glaser & Glaser, 1988; O’Leary, 1990). In addition, relatively few studies have simultaneously demonstrated actual health changes in individuals with immunologic alterations (Herbert & Cohen, 1993; Kiecolt-Glaser & Glaser, 1995; O’Leary, 1990). This has resulted in a low incidence of clinical endpoints in various populations and a lack of power to test hypotheses in these populations (Herbert & Cohen, 1993; Kiecolt-Glaser & Glaser, 1995; O’Leary, 1990). Although much has been published on the effects of stress using a PNI framework, it is apparent that more is known about the effects of various stressors on the immune system than is known about the long-term immunological consequences of biobehavioral interventions (Kiecolt-Glaser & Glaser, 1992, 1995). To make further advances in the study of chronic stress on health outcomes, the use of more prospective, longitudinal designs should be
implemented, which include assessments of parameters, such as current health and nutritional status, use of alcohol, medication, smoking and caffeine intake, sleep, and physical activity. The evaluation of these parameters and making them a routine part of a research protocol may help control some of the error variance that may be caused by these parameters and provide a clearer picture in understanding the interaction between the Central Nervous System (CNS) and immune system. (Herbert & Cohen, 1993; Kiecolt-Glaser & Glaser, 1988, 1995; O'Leary, 1990).

**Stress Reduction in HIV-1 Infected Individuals**

The psychological and physical impact of HIV-1 infection, the challenges of managing HIV disease, and the evidence that one's coping ability can greatly influence both of these health outcomes have led to research evaluating the effects of nonpharmacologic interventions in combating the progression of HIV-1 infection. The study by Coates, McKusick, Kuno, and Stites (1989) was one of the first published intervention studies that evaluated the impact of stress management training on sexual behavior and immune function in 64 gay men infected with the HIV-1 virus. The subjects were randomized to a stress management group that met for eight 2-hour sessions and a full day retreat or to a wait list control group. A number of functional measures of immunity was measured and included NK cell activity, lymphocyte response to Con A, cytomegalovirus (CMV), Candida antigen, and serum immunoglobulin A (IgA). The study concluded that, although there were no differences between the treatment and wait list control subjects in lymphocyte number and function, the subjects
in the intervention group reported significantly fewer sexual partners. The failure to find changes in the immune outcomes was attributed to such factors as (1) the possibility of sadness associated with termination of the group may have influenced the post-treatment measures, (2) single measurements of immune function may have been insufficient, (3) immune function may not have been influenced by stress in the presence of HIV, and (4) the intervention may not have been potent enough to modify immune function. Moreover, the impact of the group on psychological distress was not systematically evaluated. Furthermore, because the controls for baseline lymphocyte levels, health status, and potential cofactors were minimally described in the study, the impact of such confounding factors as stage of illness, antiretroviral medications, and the use of psychoactive substances cannot be sufficiently judged for this study (Chesney & Folkman, 1994; McCain & Zeller, 1996).

The use of cognitive behavioral stress management interventions (CBSM) has been successful as a stress reduction technique and has had beneficial effects on immune status in individuals infected with HIV-1. Several studies have used the CBSM intervention in an attempt to buffer the potential psychological and physiological effects of HIV-1 infection. In a study evaluating the effectiveness of group intervention on newly diagnosed people with AIDS, 50 men were randomly assigned to either a 10-week cognitive-behavioral intervention or to a comparison group (Fawzy, Namir, & Wolcott, 1989). The cognitive-behavioral intervention consisted of stress management skills, relaxation techniques, and problem-solving skills. The men in the cognitive-behavioral group reported greater reductions in anxiety and depression than those in the comparison
In contrast, a study using both psychological measures of distress and immune function with HIV-1 was used to evaluate 47 asymptomatic, healthy gay men randomly assigned to a CBSM group or to an assessment-only control group 5 weeks before being notified of their HIV-1 serostatus (Antoni, Baggett, Ironson, LaPerriere, August, Klimas, Schneiderman, & Fletcher, 1991). Seventy-two hours before and 1 week after serostatus notification, blood samples and psychometric data were collected. The seropositive control subjects showed significant increases in depression, but only slight decrements in lymphocyte proliferation response to PHA and lymphocyte cell counts prenotification to postnotification of seropositivity. The seropositive CBSM subjects did not show significant pre- to post- changes in depression, but did show significant increases in T-helper and NK cell counts and a slight increase in lymphocyte proliferative responses to PHA compared to the control group. In conclusion, the authors suggested the need that the study’s findings be compared to longitudinal studies that document changes in health status (e.g., the appearance of symptoms related to opportunistic infections) before any claims of health enhancement can be made for the use of CBSM interventions on HIV-1 infected individuals (Antoni et al., 1991).

Exercise training may also serve as an alternative behavioral intervention for stress reduction in HIV disease. Several studies have evaluated the effects of aerobic exercise on psychological and immunological measures in HIV-1 infected individuals (LaPerriere et al., 1990; MacArthur, Levine, & Birk, 1993; Rigsby, Dishman, Jackson,
Maclean & Raven, 1992). MacArthur et al. (1993) and Rigsby et al. (1992) documented the positive effects of a chronic, submaximal exercise regime on buffering psychological distress and improving immune function in HIV-1 infected individuals. LaPerriere et al. (1990) explored the use of acute, submaximal exercise on the cardiovascular system and lymphocyte count and perceived sense of well being in HIV-1 infected individuals. The term chronic and acute refer to the time duration of an exercise program, with chronic lasting a duration of approximately 10-24 weeks, and acute being less than 10 weeks (Åstrand & Rodahl, 1986). A summary of these studies and subsequent implications on future stress management research will be presented.

MacArthur et al. (1993) explored the effects of a 24-week aerobic exercise program on T-helper cell count, cardiovascular fitness and perceived sense of well being in 25 men with HIV-1 infection. The subjects were randomly assigned to a low intensity or high intensity group. At the end of the 24-week intervention, only 6 exercise subjects (high intensity, n = 3; low intensity, n = 3) remained in the study. That there was no inclusion or exclusion criteria other than seropositivity for HIV was cited as the major reason for subject drop-out. The authors noted that a fair majority of the subjects quit the study due to fatigue or being hospitalized for illnesses related to severe immunodeficiency. Although the authors recognized that the small number of subjects and lack of control group would prevent the making of definitive conclusions, they found that the 6 subjects showed a 15-20% improvement in aerobic power and overall improvement in cardiovascular fitness, an increase in T-helper cell count, and reported low anxiety and depression.
In addition, Rigsby et al. (1992) evaluated the effects of exercise on 37 asymptomatic HIV-1 men. Subjects were randomly assigned to a 12-week exercise training program that met three times a week or to a counseling only group. The exercise group showed increases in cardiovascular fitness and demonstrated a trend toward an increase in T-helper cell number compared to subjects in the counseling only group. Both exercise and counseling groups showed significant decreases in depression pretest to posttest.

LaPerriere et al. (1990) evaluated the effect of an aerobic exercise training intervention on attenuating psychological distress and immune decrements accompanying the notification of serostatus in 50 asymptomatic gay males. The men were randomly assigned to an aerobic exercise condition or a measurement-only control group. Blood samples and psychosocial data were collected 3 days before and 1 week after serostatus notification. The exercise group showed an increase in T-helper cell number and a decrease in anxiety and depression compared to the control group. The authors concluded that exercise was effective in buffering the adverse effects of HIV-positive serostatus notification on mood state and immune function.

Although the data for the use of exercise as a stress-management technique are limited, the aforementioned studies suggest a common theme, i.e., that the use of exercise training as a behavioral intervention for people with HIV-1 infection can provide psychological and immunological benefits to this population. Two major biases potentially confound the findings of these studies: the majority of the subjects were men, and a specific inclusion criteria was not used. MacArthur et al. (1993) had no inclusion
criteria, Rigsby et al. (1992) used the modified Walter Reed criteria, and LaPerriere et al. (1990) used the CDC recommendations. More research is needed in order to assess the potential influences that such an intervention may have on HIV disease progression.

**Outcome Measurement of Stress**

The use of salivary and serum cortisol as a measure of both acute and chronic stressors has been documented throughout the psychobiological and exercise literature (Antoni et al., 1992; Calbet, Navarro, Barbany, Manso, Bonnin, & Valero, 1993; Del Corral, Mahon, Duncan, Howe, & Craig, 1994; Kirschbaum & Hellhammer, 1989; McDowell, Hughes, Hughes, Housh, & Johnson, 1992; O'Connor and Corrigan, 1987; Stupnicki & Obminski, 1992). The use of saliva to measure cortisol has several advantages: collection can be done at home, the collection technique is simple to teach to subjects, collection is inexpensive, multiple samples can be obtained easily, and there is no need for venapunctures (Ellison, 1988; Kahn, Rubinow, Davis, Kling, & Post, 1988; Kirschbaum & Hellhammer, 1989; Landon, Smith, Perry, & Al-Ansari, 1982; Vining & McGinley, 1987; Vining, McGinley, Maksvytis, & Ho, 1983). Landon et al. (1982) discussed several disadvantages of using salivary cortisol as a measurement of HPA axis function. First, there was a problem of emotive bias. The researcher may be reluctant to ask subjects to provide a saliva sample because they assume that the patient would chose to have a venapuncture instead. This hesitation may have contributed to the fear of the researcher contracting tuberculosis. Recent research supports that it is safer to handle saliva than blood because it decreases the potential exposure to hepatitis
and the HIV virus (Kalichman, 1995; Osmond, 1990). Additionally, there is the concern that salivary flow rate may affect cortisol levels. Subsequent studies on this issue have demonstrated that saliva flow rate does not influence salivary cortisol levels (Vining & McGinley, 1987; Vining, McGinley & Symons, 1983; Walker, Riad-Fahmy, & Read, 1978). The development and availability of an adequately sensitive assay specifically for salivary cortisol measurement also concerned researchers. Landon et al. (1982) pointed out that “all radioimmunoassays are sufficiently sensitive (to detect cortisol levels in saliva) but the available, commercial, cortisol kits have been optimized for plasma” (p. 301). However, several studies suggest that the simple modification of commercial kits designed for the assay of cortisol in serum and urine will allow for rapid and direct detection of cortisol in saliva at a relatively low cost (Aardal & Holm, 1995; Al-Ansari, Perry, Smith, & Landon, 1982; Riad-Fahmy, Read, & Walker, 1983; Tunn, Möllmann, Barth, Derendorf, & Krieg, 1992; Walker et al., 1978).

The use of saliva as opposed to plasma as a measure of HPA axis activation has been demonstrated to be a reliable and valid reflection of biologically active cortisol in plasma. Serum cortisol can be difficult to interpret because of the presence of corticosteroid-binding globulin (CBG), serum proteins, and albumin (Kirschbaum & Hellhammer, 1989; Rolih & Ober, 1995; Vining et al., 1983b). Approximately 90% of serum cortisol is bound to CBG, with the remaining 5-10% of the hormone unbound or “free” (Kirschbaum & Hellhammer, 1989.) The unbound hormone is considered to be biologically active, resulting in the many aspects of growth, metabolic, and physiologic functions (Kirschbaum & Hellhammer, 1989; Rolih & Ober, 1995; Vining et al., 1983a,
Salivary cortisol levels are unaffected by CBG, thus reflecting the biologically active form of the hormone and suggesting a more appropriate measure of the assessment of adrenal status versus serum cortisol (Kirschbaum & Hellhammer, 1989; Vining et al., 1983a, 1983b).

In considering the advantages and disadvantages of salivary steroid measurements, a key point to consider is that the accuracy of the salivary cortisol measurement relies on the quality of the sample. Minor blood or food contamination may significantly alter results. Because of the differences in the amount of biologically active hormone in saliva versus serum, contamination of the saliva with blood would falsely elevate cortisol levels. Elevated cortisol levels can result from blood and exogenous steroids from food contamination, medications, or other ingested substances. Subjects with mouth bleeding should not be used. Possibility of contamination may be eliminated by having subjects waiting 15-30 minutes after eating and rinsing the mouth well before collecting a saliva sample (Ellison, 1988).

Several studies have documented the immunosuppressive effects associated with an elevation in cortisol levels as the result of a physiological or psychological stressor (Antoni et al., 1990; Calabrese et al., 1987). An increase in cortisol production causes an atrophy of lymphoid tissue, resulting in a decrease in lymphocyte number and percentage and subsequent suppression of the immune system (Calabrese et al., 1987).
Cortisol and Physical Stress in Non HIV-1 Infected Individuals

Cortisol increases in response to various types of physical and psychological stresses and exercise. Researchers have used various methods to elucidate spontaneous cortisol secretory episodes and to relate this increase in cortisol production to an individual's mood, cognition, and behavior (Kirschbaum & Hellhammer, 1989). However, there are several methodological issues in acquiring blood samples for cortisol measurement, including the emotional bias and inconvenience of multiple sampling, cost, equipment, and personnel needed for laboratory expense. The use of salivary cortisol has been a more appropriate measure of HPA axis function than serum cortisol (Ellison, 1988; Kahn et al., 1988; Vining et al., 1983a).

Stahl & Dörner (1982) were the first to monitor salivary cortisol levels in 26 patients after painful medical procedures such as prostatic biopsy, cystoscopy, and sternal puncture. The magnitude of cortisol response was 157%, 181%, and 203% above baseline values, respectively. In a painless stress model, Tarui and Nakamura (1987) assessed the effect of head-to-toe gravitation acceleration (Gz) on cortisol levels in four healthy non-aircrew volunteers. On three days, the subjects were exposed to acceleration stress of +3 Gz, +4 Gz, and +5 Gz without a G-suit for 1 minute. The authors noted that, at the maximal stress of +5 Gz, cortisol levels were elevated threefold in all subjects. The results of the study supported earlier findings suggesting a severity-dependent increase in cortisol (Tarui & Nakamura, 1987).

Several studies have assessed the effect of various types of exercise on salivary cortisol levels (Kindermann, Schnabel, Schmitt, Biro, Cassens, & Weber, 1982;
McDowell et al., 1992). O'Connor & Corrigan (1987) examined the response of salivary cortisol to acute, submaximal exercise in 8 male volunteer subjects. For three days, the subjects exercised on a bicycle ergometer at 75% of their $\text{VO}_{2\text{max}}$ for 30-minute sessions. On the fourth day, the subjects rested quietly as the control condition. On all four days, five serial samples of serum and salivary cortisol levels were obtained at 15-minute intervals before, during, and after exercise. The researchers found high correlations between serum and salivary cortisol ($r = 0.93$) and that both serum and salivary levels increased immediately post-exercise and 15 minutes after recovery. The physiological rationale for this response was attributed to the intensity of the exercise being greater than 60% $\text{VO}_{2\text{max}}$, which produced an increase in cortisol levels that may be seen up to 20 minutes post-exercise. Kindermann et al. (1982) showed similar findings, examining the effect of a single bout of running exercise compared to prolonged aerobic running exercise on selected hormones, including cortisol, in 17 male physical education students. In conclusion, the short-term, high intensity exercise showed a marked increase in salivary cortisol compared to that of the prolonged exercise and progressive exercise to exhaustion. The authors attributed the increase in cortisol and other hormones to the similar physiologic phenomena noted in previous studies (O'Conn & Corrigan, 1987).

A study that examined the effects of chronic, maximal exercise on salivary immunoglobulin A (s-IgA) and cortisol differs from that of the previously mentioned studies. In this study, the intervention lasted 10 weeks, and the participants exercised at 70% to 80% of their $\text{VO}_{2\text{max}}$. The authors found that salivary cortisol levels and s-IgA
were decreased pre-exercise to post-exercise in the low and high intensity exercise groups. The mechanism as to why the cortisol levels decreased in the low and high intensity across the training periods is unknown, and the need for further study was acknowledged.

**Cortisol and Psychological Stress in Non HIV-1 Infected Individuals**

Research has shown that psychological situations, such as novel, unexpected, or uncontrolled situations, are associated with an increase of cortisol secretion. However, the literature on psychological stress and cortisol suggests that cortisol release is dependent on two factors: emotional ego involvement and suspenseful anticipation of noxious events (Kirschbaum & Hellhammer, 1989).

Several stressful situations are associated with an increase in cortisol production (Bassett, Marshall, & Spillane, 1987; Ben-Aryeh, Roll, & Kahana, Malberger, Szargel, & Gutman, 1985; Jones, Copolev, & Outch, 1986; Harris, Cook, Warner, Read, Walker, Thomas, & Riad-Fahmy, 1988). For example, Bassett et al. (1987) reported an increase in salivary cortisol levels in bank employees who had to deliver a 15-minute lecture in front of an audience. This elevation in cortisol levels remained for a period of 2 hours. Unfortunately, the authors obtained samples only prior to and after the public lecture so no time assessment of cortisol fluctuations could have been documented. Collection of salivary cortisol fluctuations could have provided data on whether the peak cortisol values were reached before, during, or following the stressful task.
The stress of academic examinations is also associated in an increase in cortisol production. Forty medical students obtained three different saliva samples (at different times of the day) 3 days before a test and on the day of an examination (Jones et al., 1986). Samples taken immediately prior to the test showed a significant increase in cortisol compared to the control day.

In contrast, Harris et al. (1988) compared salivary cortisol levels in 95 psychiatric patients before and after venapuncture and found no difference in mean salivary cortisol levels; however, is important to point out that cortisol levels were assessed only once following venapuncture. Moreover, methodological issues may have had an effect on the outcome, such as the unavailability of information on the elapse of time between venapuncture and sampling, that most patients were on daily tranquilizers, and that the subjects had been inpatients for 2 weeks of longer and had experienced venapuncture several times before.

These studies demonstrate that an individual’s perception of an event, as well as uncontrolled situations, are contributing factors that may increase cortisol secretion in response to stressful psychological variables. Further research is needed to evaluate the repeated effects of psychological stressors on salivary cortisol levels.

Cortisol in HIV-1 Infected Individuals

HIV-1 infection and the subsequent progression to AIDS have profound effects on virtually every organ in the human body. Research on the effects of HIV/AIDS on various body systems has shown that patients with this disease are susceptible to
endocrine and metabolic abnormalities throughout the syndrome. Potential causes for the pathogenic effects of HIV/AIDS on the endocrine and metabolic systems include compromise of endocrine tissue by hemorrhagic, infectious, or neoplastic processes; alterations in hormonal secretion or action by HIV infection; and interference with hormonal secretion or action by antibodies, cytokines, or other active molecules (Grinspoon & Bilezikian, 1992). The relationship between HIV disease and the endocrine system can range from subtle abnormalities in hormone secretion to metabolism to overt failure of the adrenal glands, which rarely occurs (Grinspoon & Bilezikian, 1992). Hormonal dysfunction may manifest itself through high serum cortisol levels despite normal ACTH levels, an altered cortisol circadian rhythm, or a reduced cortisol response to ACTH stimulation. In HIV-1 infection, the mechanisms of the dysregulation of the HPA axis are not clearly understood. Research suggests that the abnormal secretion of cortisol in HIV-1 infection is due to the secretion of two cytokines, IL-1, and interferon. HIV-1 infected monocytes release IL-1 and interferon, cytokines that have been shown to stimulate hypothalamic secretion of CRH. An increase in the secretion of CRH could lead to the increase in cortisol that occurs in some HIV-1 infected individuals (Aron, 1989; Grinspoon & Bilezikian, 1992). Conversely, the adrenal function in HIV-1 infected individuals could be suppressed as a result of polyclonal B-cell activation and the production of anti-adrenal cell antibodies. However, the specific mechanisms of these antibodies are unknown (Aron, 1989; Grinspoon & Bilezikian, 1992).
Research findings examining cortisol secretion in HIV-1 infected individuals are varied because of the proposed effects of the HIV retrovirus on the endocrine system. Two studies evaluated glucocorticoid function in HIV-1 patients using exogenous intravenous ACTH stimulation and Ovine CRH tests (Azar & Melby, 1993; Verges, Chavanet, Desgres, Vaillant, Waldner, Brun, & Putelat, 1989). Verges et al. (1989) investigated glucocortical function in 63 patients (men, n = 51; women, n = 12). HIV-1 patients were divided into Group II (asymptomatic, n = 13), Group III (lymphadenopathy, n = 27), and Group IV (clinical manifestations, n = 23). Plasma ACTH and cortisol were measured before and after administration of intravenous exogenous ACTH stimulation in the 63 HIV patients as well as in 30 age-matched, healthy volunteers. An increase in ACTH and basal cortisol levels was found in the asymptomatic and lymphadenopathy group, suggesting the early dysregulation of the adrenocortical axis in HIV infection. Only one person from the clinical manifestations group had a blunted cortisol response after ACTH stimulation. In a similar study by Azar & Melby (1993), HPA axis function was evaluated in 25 non-AIDS patients, using ovine CRH administered intravenously and followed for 120 minutes. The authors found that 13 patients had normal cortisol response, 6 patients had reduced cortisol response, and 6 patients had normal ACTH with reduced cortisol response. The study concluded that approximately 25% of the non-AIDS HIV patients had reduced pituitary reserve (blunted ACTH and cortisol responses) with high basal ACTH and cortisol; 25% of the patients had reduced adrenal reserve (normal ACTH with blunted cortisol response to CRH); and 50% maintained normal HPA axis activity with increased cortisol secretion.
A suggested rationale of this phenomenon was the increased production of CRH by the
hypothalamus that is known to occur in HIV disease.

Additional studies have evaluated cortisol secretion in HIV-1 infected individuals.
However, findings among the study populations are varied, with an increase or decrease
in cortisol production related to the abnormal function of the HPA axis in HIV-1
infection (Antoni, Schneiderman, Klimas, LaPerriere, Ironson, & Fletcher, 1991;
Gorman, Kertzner, Cooper, Goetz, Lagomasino, Novacenko, Williams, Stern, Mayeux,

In a previously cited study, Antoni et al. (1991) evaluated psychological distress,
and plasma cortisol in 71 gay men 5 weeks preceding and following notification of HIV-
1 serostatus. The authors reported a disparity in predicted relationships among distress
and cortisol. Among the HIV positive men, plasma cortisol levels were negatively
correlated with psychological distress. Again, these patterns were associated with that
of the dysregulation of the HPA axis function found in HIV-1 infection. Gorman et al.
(1991) evaluated the HPA axis function of 113 HIV+ men and 77 HIV- men by
collecting urine over a 24-hour time period for free cortisol. Significant, positive
correlations were found between cortisol level, level of depression, and level of anxiety
in the HIV positive group. No relationships were found between cortisol level and the
number of T-helper and T-suppressor lymphocytes or the T-helper to T-suppressor ratio.

The aforementioned studies documented the various effects of HIV-1 infection
on cortisol secretion and proposed several physiological mechanisms to explain the effect
of HIV-1 on the adrenal system. More research is needed in patients with advanced HIV
infection to identify those at increased risk for developing adrenal and/or pituitary abnormalities and to try to gain a better understanding as to the HPA modulatory effects on the immune systems in patients with HIV-1 infection. Research related to the reduction of cortisol levels, particularly in the HIV-1 population, would prove to be beneficial because the immunosuppressive effects of cortisol on T lymphocytes.

Quality of Life in Non HIV-1 Infected Individuals

The effect of chronic illness on the multi-dimensional concept of quality of life has increasingly become a focus of research in the health care field (Leplège & Hunt, 1997). The growing interest of quality of life in research can be attributed to several reasons. First, quality of life is used to justify or deny various forms of medical treatment. At one time, endpoints, such as rate of survival and response and duration of treatment, were used to evaluate the efficacy of medical treatments (Goodinson & Singleton, 1989; Leplège & Hunt, 1997; Stewart, Hays, Wells, Rogers, Spritzer, & Greenfield, 1994). Medicine has come to the realization that the potential side effects of many therapeutic procedures may impact an individual’s life. In addition, quality of life is used to resolve the debate about whether to treat certain conditions (Goodinson & Singleton, 1989; Leplège & Hunt, 1997; Stewart et al., 1994). Through the use of quality of life studies, comparisons are made regarding the efficacy of various treatments and the consequences that the treatments may have on the life of a person. Moreover, quality of life is used to provide a basis for the rationale of allocating resources of those
treatments found to be most cost effective (Goodinson & Singleton, 1989; Leplège & Hunt, 1997; Stewart et al., 1994).

The impact of a chronic illness on quality of life has been documented in the literature (Anderson & Ferrans, 1997; Da Silva, Marquis, Deschaseaux, Gineste, Cauquil, & Patrick, 1997; Ettigi, Meyerhoff, Chirban, Jacobs, & Wilson, 1997; Stewart et al., 1994; Vale, Reardon, & ZuWallack, 1993). Although the studies vary in terms of type of chronic disease and study population, several common themes emerge. First, chronic illness has profound psychological, economic, social, spiritual, and physical ramifications, all ultimately affecting quality of life. In addition, interventions such as various types of physical activity may help improve quality of life in chronic illness.

In a descriptive study to describe quality of life in people with chronic fatigue syndrome (CFS), Anderson and Ferrans (1997) reported that CFS significantly impacted every aspect of quality of life, such as impaired health and physical function, poor social and family relationships, and economic and spiritual distress. Similarly, Ettigi et al. (1997) found an increased rate of unemployment; impairment in emotional well being, physical function, and social relationships; and overall poor self esteem in people with panic disorders. In a study of quality of life in patients with benign prostatic hyperplasia (BPH), investigators found concerns in the ability of maintaining sexual function, feelings of inadequacy, and worry about the ability of performing activities of daily living (Da Silva et al., 1997).

Vale et al. (1993) evaluated the effects of outpatient pulmonary rehabilitation on exercise performance and quality of life in 71 patients with chronic obstructive disease.
The authors found significant improvements in exercise endurance and scores on the chronic respiratory disease questionnaire (a quality of life measure) and pre- to post-participation in the intervention. In a 2-year longitudinal study evaluating the effects of physical activity on exercise in patients with chronic conditions (e.g., hypertension, recent myocardial infarction, and diabetes), Stewart et al. (1994) found that exercise was associated with improvements in physical function, energy/fatigue, and mental health, decreases in depression and anxiety, and feelings of psychological well being in the 1,758 study participants.

In conclusion, chronic illness has a potential negative impact on quality of life. There is a continuing need to identify and measure specific quality of life issues and develop interventions that will help patients cope more effectively with their illnesses.

Quality of Life in HIV-1 Infected Individuals

Ultimately, it is the hope of researchers and those infected with the HIV virus that a cure will be developed. Although life expectancy has been greatly increased with the development and combination of drug therapies such as anti-retroviral and protease inhibitor medications, inevitably HIV-1 infected individuals will experience a decline in immune status and eventual death (Kalichman, 1995). The issue of quality of life has become an increasingly important one in the planning and implementation of treatments and stress management programs for HIV-1 infected individuals. The concept of quality of life has been discussed in-depth in many aspects of the scholarly literature; however, little has been done to measure and define this concept among patients who are HIV-1 infected.
infected (Cleary, Fowler, Weissman, Massagli, Wilson, Seage, Gatsonis, & Epstein, 1993; Copfer et al., 1996; Revicki et al., 1993). Similarly, little is known of the effects of age, ethnicity, sex, and stage of HIV-1 disease progression on quality of life (Holzemer & Wilson, 1995; Leplège & Hunt, 1997). Although some HIV-1 infected individuals are able to adapt to their illness without experiencing stress or a decrease quality of life, several studies have explored the perceptions and the multidimensionality of quality of life in HIV-1 infected individuals (Chesney & Folkman, 1994; Chuang, Devins, Hunsley, & Gill, 1989; Coward, 1994; Nott & Vedhara, 1995; Siegal & Krauss, 1991; Thompson, Nanni, & Levine, 1996; Turner & Lloyd, 1995).

Initially, research in quality of life among HIV-1 infected individuals has focused on the anxiety and depression experienced by these individuals. Chesney & Folkman (1994) reported that quality of life among people with HIV-1 infection is often mentally and physically overwhelming. The decision to disclose HIV-1 serostatus and the circumstances by which disclosure occurs can have profound effects on the lives of this population. With issues such as public misinformation and the fear and stigma associated with a positive diagnosis, HIV-1 infected people are faced with overt and covert forms of discrimination. Moreover, there is a substantial increase in the need to seek medical care that may involve participation in clinical drug trials, experimental prophylactic therapies, multiple physician visits, and laboratory tests. These treatments may be very disruptive to the life of an HIV-1 individual, especially regarding the need to balance the sometimes complex medical management with work and social obligations.
Similarly, in a phenomenological study of 10 men and 10 women with AIDS, Coward (1994) explored quality of life using a self-transcendence approach. Self-transcendence is defined as "...an experience during which one reached outward beyond personal concern or inward toward increased understanding [resulting] in feelings of increased connectedness with others, increased self-esteem, well being and increased purpose and meaning in life" (p. 332). She found that feelings of fear, uncertainty, aloneness, and sadness were expressed related to having AIDS. Chuang et al. (1989) examined the levels of psychosocial distress and well being in 65 gay and bisexual men infected with HIV-1. The men experienced high levels of psychosocial distress, but those with asymptomatic HIV infection were significantly more distressed than those with AIDS. The authors suggested that these findings may be related to uncertainties about the progression of the illness, fears of pain and suffering, and general apprehension of the uncertainty of the future (Chuang et al., 1989).

Psychosocial adjustment among people with HIV/AIDS has become an important focus in the quality of life literature. Research has become essential in developing appropriate interventions that will help maintain spiritual, emotional, psychological, and physiological well being, hence improving overall quality of life. Thompson et al. (1996) examined day to day stressors faced by HIV positive individuals in an attempt to identify relationships between the stressors and psychosocial coping mechanisms used by this population. The authors found that the number of stressors reported by the subjects was significantly positively (p < .05) related to the partaking of three specific behaviors:
increased alcohol consumption, cigarette smoking, and high risk sexual behavior (e.g., receptive or insertive anal sex without a condom).

Siegel and Krauss (1991) found several beneficial coping strategies for maintaining physical and emotional health in HIV-1 infected individuals. These measures included adapting a holistic approach to good health (e.g., avoiding tobacco, alcohol, getting adequate rest), maintaining an appropriate vigilance about one's health (such as avoiding a panic over new symptoms or infections and maintaining emotional equilibrium defined as a positive psychological state). The authors concluded that there was a need for more longitudinal studies to demonstrate how these and other adaptive behaviors may change over the course of HIV-1 disease.

The measurement of quality of life continues to be a subject of debate in the literature. Issues are currently being explored, such as what type of instrument best captures quality of life and what dimensions adequately assess quality of life (Holzemer & Wilson, 1995). Further, the quantification of quality of life presents with several methodological problems. First, who should measure quality of life, the subject, caregiver, or medical personnel? Second is the development of a simple, reliable, and valid instrument. Ideally, the instrument should be easy and quick to administer, simple to comprehend by the subject, and sensitive enough to detect the benefit of one intervention versus another (Goodinson & Singleton, 1989; Holzemer & Wilson, 1995).

The Medical Outcomes Survey-HIV (MOS-HIV) (Wu et al., 1991) was used to assess quality of life in this study (Appendix B). The MOS-HIV is a 35-item questionnaire (Medical Outcomes Trust, 1997) that is a modification of the Medical
Outcomes Short-form [SF-20] and MOS-HIV 30-item questionnaire (Stewart, Hays, & Ware, 1988; Wu et al., 1991). A high score on the MOS-HIV indicates lower symptomatology and overall better health. Although there are several quality of life questionnaires in the literature (Quality of Well Being Scale and Sickness Impact Profile) that are currently used in the HIV-1 population, these instruments tend to be tedious, long (20-45 minutes to complete), and accused of failing to capture the multiple dimensions associated with HIV disease (Wu et al., 1991). The MOS-HIV uses Likert-type scales and takes less than 5 minutes to complete (Cofer et al., 1996; Holzemer & Wilson, 1995; Revicki et al., 1995; Wu et al., 1991). The survey contains six health concepts from the initial MOS SF-20 and five additional concepts specific to HIV. The initial six scales include physical functioning (6 items), role functioning (2 items), social functioning (1 item), mental health (5 items), health perceptions (5 items), and pain (2 items). The five additional items are thought to be relevant to individuals who are infected with the HIV virus and include energy/fatigue (4 items), cognitive function (4 items), health distress (4 items), quality of life (1 item), and overall health (1 item) (Burgess, Dayer, Catalan, Hawkins, & Gazzard, 1993; Holzemer & Wilson, 1995; Wu et al., 1991).

Cronbach’s alpha reliability measures for the MOS-HIV ranged from .78 to .91 for the 11 subscales in HIV-1 infected populations. Construct validity was established through correlations with the Health-Related Quality of Life questionnaire and by the demonstration of decreased quality of life scores with HIV disease progression (Burgess et al., 1993; Holzemer & Wilson, 1995; Revicki et al., 1995; Rizzi, Marchesi, Morelli,
Wu et al. (1991) tested the reliability and validity of the MOS-HIV in a sample of 117 subjects (73 with asymptomatic HIV infection and 44 with symptomatic HIV disease). The study concluded that the MOS-HIV was indeed sensitive enough to detect differences between the asymptomatic and symptomatic subjects with HIV-1 infection. Specifically, asymptomatic subjects had significantly better overall health, physical function, role function, and less pain compared to symptomatic subjects. In a sample of 99 HIV-seropositive gay men, Burgess et al. (1993) examined the reliability and validity of the MOS-HIV. Cronbach's alpha reliability measures ranged from 0.78 to 0.90 for the 11 subscales. In this study, construct validity was established through correlations with the HIV-related Quality of Life questionnaire (HIV-QOL) that demonstrated a decrease in QOL with disease progression.

Wachtel, Piette, Mor, Stein, Fleishman, and Carpenter (1992) utilized the MOS-HIV to examine the quality of life of 520 HIV-1 infected subjects who were participants in the AIDS Health Service Program (AHSP). The AHSP was developed to assess and facilitate the continuity of community based care for people with HIV/AIDS in 11 community-based programs throughout the United States.

Wachtel et al. (1992) reported that many aspects of quality of life are affected during the course of HIV disease, such as role functioning, social functioning, physical functioning, mental health, general health perceptions, and body pain. The effect of advanced HIV-1 disease on quality of life as defined by four or more symptoms is
greater relative to the effect of quality of life on other chronic diseases such as cancer or depression. Moreover, differences among the perceptions of quality of life change among age groups. Older people infected with HIV-1 tend to have bleaker perceptions of the health as reflected by lower physical role and social functioning scores. The study concluded that the MOS-HIV was a sensitive indicator of quality of life among HIV-1 individuals and may be a useful tool in developing therapies and implementing community and social services that may help people with HIV during the course of their disease (Wachtel et al., 1992).

The MOS-HIV has been a valuable instrument that appears to capture the complexity of the concept of quality of life in people with HIV-1. For the purposes of this study, the MOS-HIV will be used to assess the quality of life in a cohort of HIV-1 infected individuals participating in a 12-week aerobic exercise program.

**HIV, Exercise, and Immune Status**

There are several immunological and viral processes that occur during the clinical course of HIV-1. The primary target in HIV-1 infection is the T helper/inducer cell (CD4). CD4 cells play a vital role in the promotion of the function of many other cells in the immune system. CD4 cells produce lymphokines, such as interleukin-2 (IL-2), which are proteins that promote the growth and replication of other T-helper cells. In addition, CD4 cells produce the glycoprotein gamma-interferon, which increases the lytic ability of NK cells and helps protect other cells from infection (Calabrese et al., 1987; Kemeny, 1994; O'Leary, 1990).
The HIV-1 retrovirus attaches itself to the membrane of CD4 cells, enters the cell, and incorporates itself into the cell's genetic material. The CD4 cell eventually dies once the HIV-1 retrovirus begins to replicate itself (Antoni et al., 1990; Solomon, Kemeny, & Temoshok, 1991). During the course of HIV-1 infection, the loss of CD4 cells can lead to the development of opportunistic infections and other diseases that are normally resisted by a healthy immune system (Calabrese et al., 1987; Kemeny, 1994; O'Leary, 1990).

In HIV-1 infection, there is a progressive decline in the number and function of CD4 cells. With the depletion of CD4 cells, there is an increase in the absolute numbers of essentially unresponsive CD8 cells (Bollinger & Siliciano, 1992; Klatzmann, McDougal, & Maddon, 1993). The normal ratio of CD4/CD8 (2:1) drops to a ratio of less than 0.4 (Bollinger & Siliciano, 1992; Klatzmann et al., 1993; Wormser & Horowitz, 1992).

In examining and interpreting CD4 and CD8 absolute counts and percentages, several points warrant consideration. Absolute counts are derived from the percentage of CD4 cells multiplied times the total white blood cell count (WBC). Factors such as exercise, stress, and diurnal variation can cause the numbers of WBCs to vary day-to-day. The CD4 and CD8 percentages reflect the number of functioning lymphocytes and are thought of to be a better indicator of cellular immunity (Wormser & Horowitz, 1992).

Aerobic exercise training is a technique which has been widely accepted in enhancing overall health status (Keast, Cameron, & Morton, 1988; Mellion, 1985;
LaPerriere et al., 1990; Lawless, Jackson, & Greenleaf, 1995). Current researchers have shown that submaximal exercise training produces positive benefits on neuroendocrine, psychological, and immune variables in HIV-1 infected individuals (Haskell, 1987; Layman, 1974; Mellion, 1985; Spielberger, 1987). Specifically, submaximal exercise improves immune function by increasing NK cell activity, IL-1 and IL-2 levels, CD4 counts, endorphins, enkephalins, and decreases in cortisol secretion (Keast et al., 1988; Lawless et al., 1995). Although it has been recognized and documented that exercise has both beneficial and immunosuppressive effects on the immune system, the probable physiological mechanisms by which exercise brings about these effects is not fully understood (Nash, 1994).

Several studies have demonstrated that an exercise training program assists in the reduction of anxiety and depression, increases feelings of well being, and may attenuate the effects of NK cell degradation and enhance CD4 count in individuals infected with HIV-1 (LaPerriere et al., 1990, 1991; MacArthur et al., 1993; Rigsby et al., 1992).

LaPerriere et al. (1990, 1991) found that aerobic exercise training enhanced immune function and reduced psychological distress in gay men who were to be notified of their HIV-1 serostatus. LaPerriere et al. (1990) reported that seropositive controls showed significant increases in anxiety and depression and decrements in NK cell number following notification. Seropositive exercisers showed decreases in anxiety, depression, a nonsignificant increase in their CD4 counts, and no change in NK cell number. In a 10-week aerobic exercise study, LaPerriere et al. (1991) found a significant increase in the CD4 counts among seropositive exercisers. In addition, the seropositive exercisers
showed an increase in the number of CD45RA+CD4+ cells. This finding was of particular relevance in that a decline in CD45RA+CD4+ cells is associated in the acceleration of HIV-1 infection. The increases of CD4 and CD45RA+CD4+ cells are comparable to those increases observed in studies using azidothymidine (AZT) but without the side effects (LaPerriere et al., 1991).

In the aforementioned study, Rigsby et al. (1992) found that the exercise group experienced significant increases in neuromuscular strength and physical fitness, without degradation to the immune status as indicated by a decrease in CD4 counts, CD8 counts, total leukocyte, and total lymphocyte numbers. Furthermore, the authors concluded that an exercise regimen could increase physical fitness, with an improvement in performing activities of daily living as well as attenuating the characteristic muscle atrophy and nervous system disorders in HIV positive individuals.

In contrast, MacArthur et al. (1993) found no significant changes in CD4 count in the subjects who completed a moderate exercise training program. Failure to find significant immunologic changes was attributed to only six subjects completed the 24-week program. However, the authors did find improvement in cardiopulmonary fitness (e.g., improved VO$_2$ max, decreased heart rate) in the subjects who completed the intervention. The authors concluded that an exercise training regimen could benefit people who were moderately to severely immunologically compromised with HIV-1 infection.

The effects of a moderate, submaximal exercise training program on psychological and immunological variables in HIV-1 infection is promising; however, in
reviewing these studies, several questions must be considered before prescribing specific exercise interventions for HIV-1 individuals. First, what is the potential “strain” on the immune system that an aerobic exercise program could cause to a person with HIV disease? Research has shown that repeated bouts of exercise may have an immunosuppressive effect. Such suppression could lead to the development of opportunistic infections. Second, what are the effects of different exercise intensities in HIV-1 infected individuals? This question is important in deriving an exercise intensity of best efficacy. Third, what are the long-term effects of aerobic exercise training and HIV drug therapies such as antiretrovirals and protease inhibitors? The concomitant use of aerobic use and HIV drug therapies will need to be continuously evaluated to achieve the beneficial synergistic effects on immunity (LaPerriere et al., 1990, 1991, 1994).

In summary, the use of an exercise regime, in addition to such programs as stress management or dietary counseling, has the potential to be an effective means of promoting a healthy lifestyle and quality of life in HIV-1 infected patients.

**Aerobic Power in Non HIV-1 Infected Individuals**

In order for the human body to endure prolonged physical activity, the cardiovascular and pulmonary systems must be able to deliver oxygen and nutrients to working skeletal muscle (Åstrand & Rodahl, 1986; Lamb, 1984). The muscle that is working must be able to efficiently extract and use the oxygen and nutrients delivered to replenish cellular adenosine triphosphate (ATP), a vital source of energy needed for various metabolic functions (Guyton, 1991; Lamb, 1984). The delivery of oxygen from
the lungs to the body's tissues and the subsequent use of oxygen by cellular mitochondria to generate ATP are known as aerobic power (Åstrand & Rodahl, 1986; Guyton, 1991; Lamb, 1984). Aerobic power, also known as oxygen consumption, oxygen uptake, aerobic capacity, functional capacity or VO₂ max, is considered to be the "gold standard" in the measurement of maximal oxygen uptake because it is objective and highly correlated with cardiac output and physical endurance (Åstrand & Rodahl, 1986; Pollock & Wilmore, 1990).

The evaluation of aerobic fitness through maximum aerobic power (VO₂ max) has been documented in the scholarly literature. The largest amount of oxygen that a person can utilize under vigorously active exercise is a phenomenon which has been explored in many populations, such as obese military recruits, cancer patients, police officers, and older adults. Generally, aerobic exercise has improved cardiovascular fitness and muscular strength, decreased anxiety and psychological stress, and has had an overall positive effect on general well being (Lim & Lee, 1994; MacVicar & Winningham, 1986; Norris, Carroll, & Cochrane, 1990; Steinhaus, Dustman, Ruhling, Emmerson, Johnson, Shearer, Latin, Shigeoka, & Bonekat, 1990).

In a study of 40 obese recruits going through 20 weeks of basic military training, Lim & Lee (1994) found that aerobic exercise helped decrease body fat, lower heart rate and blood pressure, increased muscular strength, and promote weight loss. Norris et al. (1990) found that aerobic exercise decreased blood pressure, heart rate, and improved muscular strength in a 10-week aerobic exercise study conducted with 100 male police
officers. Additionally, exercise participants reported less job stress and increased feelings of general well being.

MacVicar & Winningham (1986) evaluated the effect of a 10-week, tri-weekly aerobic exercise program on the functional capacity of ten women with breast cancer undergoing chemotherapy. The authors reported that the women in the exercise group had a 20.7% pretest to posttest increase in functional capacity as compared to the 17.4% improvement noted in healthy, age-matched controls. In addition, the breast cancer patients who exercised reported reduced nausea symptoms and an overall improvement in their scores on the Profile of Mood States instrument, a 65-item questionnaire measuring mood and affect.

Steinhaus et al. (1990) examined the effects of a 4-month aerobic program on heart rate, blood pressure, VO$_2$ max, and physical work capacity in 28 sedentary, older adults. The authors found that the exercise group showed improvements in all listed variables as compared to the control group. Also, additional benefits were exhibited by the exercise group, such as increased social interaction, peer support, and improvement in self-esteem.

These studies suggest that aerobic exercise has the potential to improve many aspects of psychological and physical fitness in various populations. Further research should be conducted to examine the relationship between aerobic exercise, physical fitness, and mental health.
Aerobic Power in HIV-1 Infected Individuals

Current research has suggested that aerobic exercise has many psychological and physical benefits and is used frequently as part of health regimens in acute and chronic illnesses (LaPerriere et al., 1990, 1991, 1994). Aerobic exercise reduces stress, increases physical endurance, helps maintain bodyweight, and promotes mental health. In addition, aerobic exercise training in HIV-1 infection may improve aerobic power, resulting in cardiovascular fitness and a reduction in the risk and incidence of heart disease (LaPerriere et al., 1990, 1991; MacArthur et al., 1993; Rigsby et al., 1992). Collectively, these studies seem to indicate that the use of a moderate aerobic exercise program can have beneficial results physically, psychologically, and immunologically.

LaPerriere et al. (1990, 1991) found that the level of aerobic capacity increased in both seropositive and seronegative exercise subjects. After 5 weeks of exercise training, aerobic power was significantly improved for the seropositive and seronegative exercisers (LaPerriere et al., 1990). No significant changes were found in the VO$_2$ max values of the seropositive and seronegative control participants. Similarly, after 10 weeks of an aerobic exercise training program, LaPerriere et al. (1991) found that the seropositive and seronegative exercisers demonstrated significant increases in aerobic power. Rigsby et al. (1992) reported congruent findings in VO$_2$ max in their study of the effects of aerobic exercise training on 45 male volunteers. The exercise group had an overall improvement in aerobic capacity and strength, whereas the counseling group did not change on these variables. In the previously reported 24-week program by MacArthur et al. (1993), the investigators reported a significant training effect for the
remaining six subjects who completed the study as evidenced by a 24% improvement in VO$_2$ max.

In reviewing the literature on the effects of aerobic exercise in HIV-1 infected individuals, it may be suggested that these individuals can experience significant increases in cardiovascular strength and neuromuscular fitness without negative effects on the immune system as indicated by medical diagnosis. More prospective exercise clinical trials with larger population samples should investigate the effects of exercise on additional serological markers of immunity. Also, more research should explore different lengths of training and its effects on changes in VO$_2$ max in HIV-1 infected individuals. In addition, more studies examining the effects of exercise across the spectrum of HIV disease should be investigated.
CHAPTER 3
RESEARCH METHODOLOGY

Design

This experimental study examined the effect of a 12-week aerobic exercise protocol on stress state and quality of life in HIV-1 infected adults. Subjects were selected through convenience sampling in conjunction with the parent study (Smith et al., 1994). Random assignment was conducted at The Ohio State University AIDS Clinical Trial Unit by the research pharmacist from random permuted blocks of 2 and 4. Specifically, a table of random numbers was used to randomly assign each individual to either the experimental or control condition. All subjects enrolled in the parent study between September 1996 and June 1997 were eligible for inclusion in this sub-study.

Subjects

Inclusion criteria were those of the parent study: (1) females and males between the ages of 18-50, (2) documentation of HIV infection by ELISA and confirmatory Western Blot, (3) CD4 count of 200-499, no uncontrolled endocrine or uncontrolled chronic disease, (4) no musculoskeletal limitations, (5) negative serum pregnancy test, (6) no concurrent participation in a structured aerobic exercise program, (7) ability to
attend tri-weekly exercise sessions for 12 weeks if assigned to the exercise group, (8) medical clearance from the AIDS Clinical Trial Unit, (9) medical clearance from the AIDS Clinical Trial Unit, (10) signed, informed consent as required by The Ohio State University Biomedical Human Subject’s Committee, and (11) weight at least 85% of the lower boundary of the recommended range of ideal body weight (Appendix C).

The exclusion criteria were: (1) history of or current symptoms suggesting an AIDS-defining illness, (2) pregnancy; (3) current drug abuse, (4) uncontrolled cardiac or pulmonary disease, (5) concomitant medication with appetite stimulants, such as dronabinol or megestrol acetate, and (6) platelets less than 75,000/mm³, hemoglobin less than 10g/100ml for women and 12g/100ml for men.

**Sample Size**

A power analysis was conducted for both research questions proposed by this study using the means, confidence intervals, and standard deviations of salivary cortisol levels and MOS-HIV subscale scores reported in previous studies. The projected sample size of 25 subjects enabled detection of a large effect size ($R^2 = .30$) in the physical and mental health summary scales of the MOS-HIV (alpha = 0.05, power = 80%, 1-way ANOVA). The sample of 25 subjects was sufficient to detect a large effect size for the interaction of exercise on cortisol levels across 8 timepoints using repeated measures ANOVA (group by time interaction, $R^2 = .36$, alpha = 0.05, power = 75%) (Cohen & Cohen, 1983).
Setting

Recruitment and pretest and posttest questionnaires were conducted at The Ohio State University ACTU, which is one of the 35 adult units funded by the National Institutes of Health (NIH), to conduct trials of experimental therapies for HIV-1 infection and its related opportunistic infections and malignancies. The ACTU is staffed by 7 nurses, 1 social worker, 1 pharmacist, and 4 data/clerical personnel.

The graded exercise tests are being conducted in the laboratory of Dr. David Frid (study consultant) at the OSU Hospitals. The subjects of this study were exercised in conjunction with the OSU faculty/staff fitness program and the OSU Cardiac Rehabilitation Program. Subjects in this study will exercise with patients, faculty, and staff exercising in classes which are part of the above program (Smith et al., 1994).

Subject Recruitment and Entry into Study

As noted, the OSU ACTU cohort served as the primary recruitment source. Founded in 1987, the cohort has enrolled 1,500+ subjects (36% with CD4 counts of 200-400) as of 1996 (Smith et al., 1994). Approximately 30 new subjects enroll monthly. Potential participants were approached regarding the enrollment into the exercise cohort. The publicizing of the study to potential audiences (e.g., gay bars, coffee shops, bookstores) was conducted through the parent study to attract participants. A special effort was made to obtain minority subjects by visiting establishments known to serve predominately minority clientele (Black churches and beauty salons).
Procedures

Data Collection Process

At the ACTU, the research nurses explained the exercise study and obtained the informed consent for the subject. If the subject agreed to participate, the investigator provided a detailed explanation of the study, including the collection of the saliva for cortisol and dietary restrictions related to saliva collection, collection technique, storage of the saliva, and a negotiated time to collect the saliva. A flyer detailing specific instructions regarding saliva collection was given to all subjects (Appendix D). Specifically, the subject was instructed not to eat, drink, or smoke for 15-30 minutes prior to saliva collection (Ellison, 1988). After a thorough rinse of the mouth with water, each subject chewed on a rubber band for 5 minutes. The subject then expectorated into a medicine cup. The investigator either picked up the saliva sample from the subject's home or met the subject at the J. Leonard Camera Center (JLCC), a rehabilitation facility. The saliva samples were transferred to a polypropylene container, refrigerated for no longer than 24 hours to prevent degradation of the cortisol hormone, and then stored at -80°C (Ellison, 1988). Plastic storage cups, rubber bands, and paper bags were provided by the investigator.

The MOS-HIV was administered during enrollment of subject into the study and then completed at Week #12 (the end of the study). Salivary cortisol was collected by the subjects at morning and evening time intervals across eight data collection timepoints (Baseline 1, Baseline 2, Weeks #2, #4, #6, #8, #10, #12). Baseline 1 was the first day of
participation in the exercise study, and saliva was usually collected on a Monday. Baseline 2 was the second sample collected during the first week of participation, and saliva was usually obtained on a Thursday or Friday of Week #1. Timepoints designated for collection were between the hours of 7:00 – 8:00 a.m. and between the hours of 5:00 – 6:00 p.m. A few days prior to each saliva collection, the subject received a phone call as a reminder of the saliva collection protocols and to schedule a meeting for the investigator to pick up the saliva.

**Scoring of the MOS-HIV**

Scoring guidelines for the MOS-HIV were obtained from Dr. Albert W. Wu, co-creator of the questionnaire. The 35-item questionnaire contains 11 dimensions or scales, with a higher score indicating better health. The items and scales are scored in two steps. First, some questions may need to be recoded. Next, the items scores are summed to form scale scores. To compare the 11 dimensions (which may have different response formats), mean scores are linearly transformed to a 0-100 scale, with 0 being the lowest score and 100 indicating the highest possible score. Linear transformation formulas are in Table 1. Further information can be obtained from Dr. Wu.
Dimension | Formula |
--- | --- |
Overall Health | \( L_{\text{overall}} = \left( \frac{100}{(25-5)} \right) \times (\text{overall-5}) \) |
Physical Function | \( L_{\text{phys}} = \left( \frac{100}{(18-6)} \right) \times (\text{phys-6}) \) |
Role Function | \( L_{\text{role}} = \left( \frac{100}{(4-2)} \right) \times (\text{role-2}) \) |
Social Function | \( L_{\text{social}} = \left( \frac{100}{(6-1)} \right) \times (\text{social-1}) \) |
Cognitive Function | \( L_{\text{cognitiv}} = \left( \frac{100}{(24-4)} \right) \times (\text{cognitive-4}) \) |
Pain | \( L_{\text{pain}} = \left( \frac{100}{(11-2)} \right) \times (\text{pain-2}) \) |
Mental Health | \( L_{\text{mental}} = \left( \frac{100}{(30-5)} \right) \times (\text{mental-5}) \) |
Energy/Fatigue | \( L_{\text{vitalit}} = \left( \frac{100}{(24-4)} \right) \times (\text{vitality-4}) \) |
Health Distress | \( L_{\text{distres}} = \left( \frac{100}{(24-4)} \right) \times (\text{distress-4}) \) |
Quality of Life | \( L_{\text{quality}} = \left( \frac{100}{(5-1)} \right) \times (\text{quality-1}) \) |
Health Transition | \( L_{\text{trans}} = \left( \frac{100}{(5-1)} \right) \times (\text{trans-1}) \) |

Table 1. Linear Transformation Formulas of the MOS-HIV (Medical Outcomes Trust, 1997).

**Radioimmunoassay Procedure**

A pilot study was conducted to refine the methodology of the radioimmunoassay procedure used to assess salivary cortisol levels using Coat-A-Count kits from Diagnostic Products Corporation (DPC), Los Angeles, California. The Coat-A-Count kit is a competitive solid-phase radioimmunoassay that can be used for measurement of cortisol in saliva, serum, and urine.

The pilot study was comprised of 5 subjects (3 females and 2 males). After instruction, all subjects produced 3 ml of saliva in the morning and 3 ml of saliva in the evening. The saliva was then stored in polypropylene tubes at -80°C.

Prior to analysis, the saliva samples were thawed to room temperature and centrifuged for 10 minutes at 3,000 rpm to precipitate any mucins and debris. Although Tunn et al. (1992) compared the different incubation procedures (i.e., overnight versus a 3-hour incubation), Diagnostic Products (the manufacturer of the Coat-A-Count kit)
indicated that either incubation period would be sufficient. In keeping with Tunn et al.’s (1992) procedures, the present study also compared the two incubation periods, which determined if there were differences in cortisol levels based on the longer versus shorter incubation time. The cortisol levels of the pilot subjects ranged from 2.7 to 4.8 µg/dL. Circadian differences were observed. In general, the 24-hour incubation yielded lower levels of cortisol. After further consultation with technical support scientists at Diagnostic Products, a 3-hour incubation period was decided upon for this study.

Human Subjects Protection

The research protocol for this study was approved by the OSU Biometical Human Subjects Committee. Prior to obtaining informed consent, subjects were advised that participation was completely voluntary and that they could withdraw from the study at any time. Confidentiality of records was maintained by coding all instruments with the subject’s code number rather than individual names. A master list of the subjects and their code numbers was stored in a locked file cabinet as part of the parent study protocol.

The risks for participating in this study were minimal. The collection and storage of saliva involved relatively benign processes that the subject could do at home. All collection materials were supplied by the researcher. The advantages of participation included potential physiological and psychological benefits of participation in an aerobic exercise program and a summary and explanation of one’s cortisol level.
**Intervention (Independent Variable)**

The independent variable in this study is a 12-week aerobic exercise training program. Members of the experimental group participated in the aerobic exercise training program, and members of the control group participated in biweekly telephone calls or clinic visits with the study staff. The control group was offered the opportunity for participation in the exercise intervention after the posttest visit during Week #12. Based on the recommendations of the American College of Sports Medicine (1991), the following aerobic exercise training protocol was used in the parent study with HIV-1 infected subjects:

1. **Exercise mode.** Cycling on a stationary cycle ergometer, walking, jogging, or running on a motor driven treadmill, or on a track dedicated to walking or running.

2. **Exercise frequency.** Three days each week.

3. **Exercise session duration.** 60 minutes (10 minutes for warm up, 40 minutes for aerobic exercise, 10 minutes for cool down).

4. **Exercise intensity/workload.** Each subject exercised using an interval training protocol that will produce a heart rate corresponding to 60% to 80% of the subject’s maximum oxygen uptake achieved on the graded exercise test (GXT) at pretest.

**Exercise Progression**

The subjects assigned to the experimental group were required to attend three 1-hour exercise sessions weekly at the OSU J. Leonard Camera Rehabilitation Center
under the supervision of an exercise trainer. With the cardiovascular and muscular adaptations that occur in response to the exercise program, the heart rate and blood pressure tended to decrease in healthy individuals in response to a given work load. The subject's heart rate response was measured continuously during exercise using a polar vantage heart rate monitor. The trainer, in consultation with the Primary Investigator of the parent study, assessed the subject's heart rate response to exercise on a weekly basis and adjusted the exercise regimen to maintain the subject's heart rate within the prescribed range.

The exercise subjects adhered to the aerobic exercise-training schedule as supported by the American College of Sports Medicine. During Week #1, the schedule consisted of a 10-minute warm-up, 20 minutes of aerobic exercise, and a 10-minute cool-down period. Week #2 comprised a 10-minute warm-up, 25 minutes of aerobic exercise, and a 10-minute cool-down. Weeks #3 - #5 consisted of a 10-minute warm-up, 30 minutes of aerobic exercise, and a 10-minute cool-down. Weeks #6 - #8 and Weeks #9 - #12 consisted of the same warm-up and cool-down periods, with an increase in the aerobic exercise sessions of 35 and 40 minutes, respectively (American College of Sports Medicine, 1991).

MOS-HIV (Dependent Variable)

The advances made in the life-expectancy of people infected with HIV/AIDS have brought forth the need for researchers to explore, develop, and document quality-of-life measures salient to this population. The MOS-HIV has been demonstrated to be
a reliable and valid measure of quality of life in HIV-1 infected individuals. (Bozzette, Hays, Berry, Kanouse, & Wu, 1995; Cleary et al., 1993; Wachtel et al., 1992; Wu et al., 1991). The MOS-HIV takes less than 5 minutes to complete and has been found sensitive in discriminating between stages of HIV disease and in detecting treatment differences in clinical trials (Bozzette et al., 1995; Burgess et al., 1993; Revicki et al., 1995; Wu et al., 1991).

There were several alternative instruments which could have been used to assess quality of life in HIV-1 infected individuals, including: the Health Assessment Questionnaire, the Visual Analogue Scale, and the Karnofsky Performance Status Scale (Holzemer & Wilson, 1995). The MOS-HIV was chosen for this study because of its ease of completion and the ability to capture various concepts that were especially salient in assessing quality of life HIV-1 infected individuals.

Salivary Cortisol (Dependent Variable)

Salivary cortisol is a inexpensive, simple, noninvasive, and valid and reliable method to measure function of the HPA axis (Ellison, 1988; Vining & McGinley, 1987; Vining et al., 1983a). Morning and evening samples reflected diurnal variations of cortisol levels. (Kirschbaum & Hellhammer, 1989; Riad-Fahmy et al., 1983; Trine & Morgan, 1995; Vining et al., 1983a). In addition, the morning and evening sample points were chosen as typical of the collection times for patients in studies of adrenal function (Vining et al., 1983a). Aardal and Holm (1995) and Vining and McGinley (1987) reported high correlations between salivary and serum cortisol levels ($r = 0.71$ to
\( r = 0.91 \). A time log recorded the collection date, time, and any observations that may have potentially affected cortisol levels. All samples were handled according to the universal precaution guidelines of the CDC (1989) for the prevention of contamination of HIV and other blood-borne pathogens.

**Subject Attrition and Incentive**

Incentives provided for the participants were restricted to those given in the parent study. Parking costs for clinic visits and exercise were paid by a voucher system. After completion of baseline tests, the experimental subjects received a $75 certificate to purchase running shoes at a store specializing in work-out shoes. Control subjects received a $75 certificate at Week #12. In addition, each experimental subject earned $1.50 for each exercise session completed during Weeks #1 - #4, $2 for each session completed during Weeks #5 - #8, and $5 for each session completed during Weeks #9 - #12. This incentive was used to maintain retention of the experimental subjects in the study. Control subjects earned $10 for each scheduled telephone call or clinic visit completed during Weeks #2 and #4, $15 for each scheduled telephone call or clinic visit completed during Weeks #6 and #8, and $25 for each scheduled telephone call or clinic visit completed during Weeks #9 - #12. Note that the incentives provided for the subjects were gradually increased over the 12 weeks to reward ongoing participation.

Two subjects dropped out of the present saliva study; one subject dropped from the parent exercise study altogether and another subject refused to provide saliva samples for the current study. Five subjects had not completed the minimum of 36
sessions required for study participation by the termination date of the sub-study 8/97. At this date, a total of 18 subjects have completed this study, including 12 controls and 6 exercisers. The six exercise subjects completing the intervention have completed a minimal of 36 sessions.

**Limitations of Methodology**

There are several limitations of this study. The participants of this study had to have a CD4 count of 200-499 (asymptomatic HIV-1 infection) as defined by the Centers of Disease Control. Thus, there may be a limitation to the generalizability of the research findings to exercise interventions in HIV-1 infected populations. In addition, although many studies report that salivary cortisol is an easy, non-invasive, reliable, and valid method to assess the HPA axis and a specific set of instructions were given for the home collection of saliva, a few subjects still had difficulty and collected sputum instead of saliva.

**Data Management**

The data of the parent study were coded, entered, and cleaned at the AIDS Clinical Trials Unit by the primary investigator of the parent study and were available for use in this project. Procedures for storage of data and maintaining patient confidentiality were approved by the OSU Biomedical Human Subjects Committee. Only coded information data were received (identifying individual subjects) to ensure confidentiality of the data retrieved from the AIDS Clinical Trials Unit.
Data Analysis

Descriptive

Experimental and control groups were compared at baseline for the demographics of age, education level, sex, and HIV risk factors to identify potentially confounding group differences. Distributions on the MOS-HIV total and subscale scores (pretest, posttest, and change scores) were assessed prior to analysis. Cortisol levels were plotted for each individual and by groups at morning and evening times to assess degree of diurnal variation.

Inferential

Mann Whitney U analyses were performed to examine the differences between groups on demographic variables and in the pretest to posttest changes in quality of life as measured by the MOS-HIV. Changes in total scores as well as actual subscale scores were assessed. For analysis of group differences in cortisol levels, cortisol values were stratified by morning and evening collection times. There were missing values of cortisol levels observed in the data; therefore, an unbalanced repeated measures ANCOVA was conducted within the morning and evening strata across the 8 data collection points (baseline 1, baseline 2, and Weeks #2, #4, #6, #8, #10, and #12). Time effects, group effects, and time by group interactions were assessed with a significant interaction term indicating group differences over time.
Statistical Software

Data were entered and verified on a computer by the researcher using the SPSS-X (Version 7.5) software data entry package at The Ohio State University College of Nursing Computer Laboratory. The data were updated as new data were entered, and a permanent database was created on disk, along with a back-up file on the hard drive of a laptop computer of the researcher. The SPSS-X software data entry package was used to perform descriptive and non-parametric analyses. The cortisol data were transferred from a hard disk to the mainframe computer at The Ohio State University Biometrics Laboratory. The software package, BMDP (BMDP Statistical Software, 1993), was used to perform the unbalanced repeated-measures ANCOVA analyses.
CHAPTER 4
ANALYSIS AND RESULTS

This chapter presents the interim data of the 18 subjects who completed the 12-week aerobic exercise study. Descriptive statistics for the experimental and control groups on demographic and health variables are presented. The findings for each research question are discussed.

Description of the Sample and Assessment of Bias from Noncompleters

Of the 23 subjects who entered the study, 18 subjects completed the study (78%). Five subjects (22%) did not complete the 36 required exercise sessions by August 1997. Demographic information on the 18 subjects who completed the study is presented in Table 2. Subjects ranged in age from 27 to 46 years, with an average age of 35.5 (SD = 5.8) in the completer group and 38 (SD = 8.1) in the noncompleter group. The 18 subjects completing the study were 12 controls and 6 exercisers. The 5 noncompleters were randomized to the exercise group. The number of sessions completed by the 5 noncompleters were as follows: Subject #1, 10 sessions; Subject #2, 14 sessions; Subject #3, 15 sessions; Subject #4, 31 sessions; and, Subject #5, 22
sessions. There were several reasons for noncompletion, which included a family crisis, medical conditions that caused a halt in exercising, and loss of interest.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Completers (n = 18)</th>
<th>Noncompleters (n = 5)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.5 5.8</td>
<td>38 8.1</td>
<td>.931</td>
</tr>
</tbody>
</table>

Table 2. Group Demographics – Age Variable

Non-parametric Mann-Whitney U analyses compared the completers and noncompleters because there were not enough subjects to assure normality of distributions of group characteristics. The small sample size and non-normality of the data violate the assumptions needed to use a parametric statistic such as the Student’s t-test. The non-parametric Mann-Whitney U technique is appropriate to detect the differences between independent groups for data at the ordinal level or higher (Munro, Visintainer, & Page, 1986). No differences were found between the completer and noncompleter groups on the variable of age (p = .931).

Differences between the completer and noncompleter groups on education level, race, risk factor, and sex were tested using contingency tables. Because of the small number of observations per cell, the assumptions of the chi-square analysis were not met, so the Fisher’s Exact test was used. No significant differences were found on any of the listed variables (education, p = 0.7743; race, p = .3950; risk factor, p = .4060; sex, p = .3950). Most of the subjects were homosexual males with at least some college
education. Two of the subjects were Black. A summary of demographic variables by completer and noncompleter groups is presented in Table 3.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Completers (n = 18)</th>
<th>Noncompleters (n = 5)</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education Level</strong></td>
<td></td>
<td></td>
<td></td>
<td>.7743</td>
</tr>
<tr>
<td>1 - 8 grade</td>
<td>2 (11%)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>9 - 12 grade</td>
<td>4 (22%)</td>
<td>1 (20%)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>13 - 16 (Undergraduate)</td>
<td>10 (56%)</td>
<td>4 (80%)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>17 - 18 (Master’s Degree)</td>
<td>2 (11%)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factor</strong></td>
<td></td>
<td></td>
<td></td>
<td>.4060</td>
</tr>
<tr>
<td>Homosexual</td>
<td>16 (89%)</td>
<td>4 (80%)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Bisexual</td>
<td>1 (5.5%)</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>1 (5.5%)</td>
<td>1 (20%)</td>
<td>2</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td>.3950</td>
</tr>
<tr>
<td>Male</td>
<td>17 (94%)</td>
<td>4 (80%)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 (6%)</td>
<td>1 (20%)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td>.3950</td>
</tr>
<tr>
<td>Black</td>
<td>1 (6%)</td>
<td>1 (20%)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>17 (94%)</td>
<td>4 (80%)</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Summary of Demographic Variables by Group Assignment (Fisher’s Exact)

**Assessment of Bias on Baseline CD4 and CD8 Absolute Counts and Percentages between Completers and Noncompleters**

To assess and compare HIV/AIDS disease state between the completer and noncompleter groups, CD4 and CD8 absolute counts and percentages were assessed using the Mann-Whitney U non-parametric test. The means, standard deviations, and p-values for CD4 and CD8 absolute counts and percentages at baseline are presented in Table 4. No significant differences were found between the two groups on baseline values for the measures given.
**Comparison of Demographic Variables by Experimental and Control Group**

Non-parametric Mann-Whitney U analyses and contingency tables were used to assess for differences between the experimental and control group on age, education level, race, risk factor, and sex. The experimental and control subjects ranged in age from 27-36 years with an average age of 39.3 years (SD = 6.4) for the experimental group and 33.6 years (SD = 4.7) for the control group. No differences were found between the experimental and control groups on the variable of age (p = .109). No significant differences were found on education level (p = .3348), race (p = 1.000), risk factor (p = 1.000), or sex (p = 1.000). Most of the experimental and control subjects were homosexual males with some college education. One of the subjects was Black. A summary of demographic variables by experimental and control group is presented in Tables 5 and 6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise Group (n = 6)</th>
<th>Control Group (n = 12)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean 39.3  SD 6.4</td>
<td>Mean 33.6  SD 4.7</td>
<td>.109</td>
</tr>
</tbody>
</table>

Table 5. Age of Subjects by Exercise and Control Group
Table 6: Education Level, Race, and Risk Factor of Subjects by Exercise and Control Group

Comparison of CD4 and CD8 Absolute Counts and Percentages between the Experimental and Control Group

A baseline comparison on CD4 and CD8 absolute counts and percentages was also conducted between the experimental and control group, utilizing the Mann-Whitney U non-parametric test. Means, standard deviations, and p-values for CD4 and CD8 absolute counts and percentages are reported in Table 7. No significant differences were found between the experimental and control group on the aforementioned variables.
Research Hypothesis #1

The first research hypothesis was that the experimental group, in comparison to the control group, would have improved scores on the MOS-HIV as a measure of quality of life over the 12-week intervention period. Analyses related to this hypothesis are discussed in the following sections.

Comparison of Pretest, Posttest, and Change Scores for the Experimental and Control Group

Non-parametric Mann-Whitney analyses were conducted to compare pretest, posttest, and change scores on the MOS-HIV between the experimental and control group. Means, standard deviations, and p-values for pretest, posttest, and change scores on the MOS-HIV are presented in Table 8. No significant differences were found between the experimental and control groups on pretest, posttest, or change scores on the MOS-HIV.

Table 7. Means, Standard Deviations, and p-Values for Baseline CD4 and CD8 Absolute Values and Percentages by Exercise and Control Group

<table>
<thead>
<tr>
<th>Variable #%</th>
<th>Control Group (n = 12)</th>
<th>Exercise Group (n = 6)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 #%</td>
<td>349 (25)</td>
<td>119.3 (13.2)</td>
<td>.494 (.682)</td>
</tr>
<tr>
<td>CD8 #%</td>
<td>1,011 (55)</td>
<td>556.0 (11.8)</td>
<td>1.000 (.820)</td>
</tr>
<tr>
<td>Variable</td>
<td>Control Group (n = 12)</td>
<td>Exercise Group (n = 6)</td>
<td>p-Value</td>
</tr>
<tr>
<td>-------------------</td>
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<td>------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td>Cognitive</td>
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<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>83</td>
<td>11.6</td>
<td>83</td>
</tr>
<tr>
<td>Post</td>
<td>82</td>
<td>18.7</td>
<td>82</td>
</tr>
<tr>
<td>Change</td>
<td>-1.3</td>
<td>13.5</td>
<td>-1.6</td>
</tr>
<tr>
<td>Distress</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>86</td>
<td>11.3</td>
<td>86</td>
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<tr>
<td>Post</td>
<td>80</td>
<td>26</td>
<td>80</td>
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<tr>
<td>Change</td>
<td>-6.7</td>
<td>19.9</td>
<td>-5.8</td>
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<tr>
<td>Mental</td>
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<tr>
<td>Pre</td>
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<td>15.8</td>
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<td>Post</td>
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<td>15.6</td>
<td>71</td>
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<td>Change</td>
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<td>11.6</td>
<td>1.3</td>
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<tr>
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<td>Post</td>
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<td>92</td>
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<tr>
<td>Pre</td>
<td>60</td>
<td>19.8</td>
<td>79</td>
</tr>
<tr>
<td>Post</td>
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<td>24.6</td>
<td>-8.0</td>
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</tr>
<tr>
<td>Pre</td>
<td>66</td>
<td>41.8</td>
<td>75</td>
</tr>
<tr>
<td>Post</td>
<td>79</td>
<td>33.4</td>
<td>83</td>
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<tr>
<td>Change</td>
<td>12.5</td>
<td>37.7</td>
<td>8.3</td>
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<td>Social Function</td>
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<tr>
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<td>90</td>
<td>8.1</td>
<td>97</td>
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<td>Post</td>
<td>88</td>
<td>23.2</td>
<td>97</td>
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<td>Change</td>
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<tr>
<td>Pre</td>
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<td>54</td>
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<tr>
<td>Post</td>
<td>67</td>
<td>32.2</td>
<td>67</td>
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<tr>
<td>Change</td>
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<tr>
<td>Pre</td>
<td>62</td>
<td>17.2</td>
<td>59</td>
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<td>Post</td>
<td>57</td>
<td>16.4</td>
<td>72.5</td>
</tr>
<tr>
<td>Change</td>
<td>-5</td>
<td>17.8</td>
<td>13.3</td>
</tr>
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</table>

Table 8. Means, Standard Deviations, and p-Values for Pretest, Posttest, and Change Scores on MOS-HIV by Experimental and Control Group
**Research Hypothesis #2**

The second research hypothesis was that the experimental group, in comparison to the control group, would have significantly lower salivary cortisol levels as a measure of stress state over the 12-week intervention period. The findings of this hypothesis are discussed in the following sections.

**Cortisol Analyses**

An unbalanced repeated measures analysis of covariance was conducted on the cortisol levels of the 18 subjects (control group, \( n = 12 \); exercise group, \( n = 6 \)) completing the exercise intervention to determine if the exercise group had significantly lower cortisol levels compared to the control group. The unbalanced repeated measures of covariance was selected for the following reasons: multiple collections of saliva were obtained during the study for each individual, missing data because of inability to collect samples at a specific timepoint, the ability to control for error variance as well as to measure group differences after controlling for other differences between subjects (BMDP Statistical Software, 1993; Munro et al., 1986). The covariate used in this analysis was the first baseline saliva sample (B1) and was chosen in an attempt to control for initial differences between the groups prior to their start in the study. The second baseline cortisol (B2) may have been influenced by the subjects learning of their group assignment and subsequent participation in the study and, therefore, was not used. The following assumptions were assessed and met before using this analysis: (1) the groups were mutually exclusive; (2) continuous data should be used for the dependent variable;
and (3) the covariate should be measured at the interval or ratio level (Munro et al., 1986). Analyses were performed to determine whether the use of a compound symmetry or an unbalanced covariance matrix structure would best fit the data. The data were run using both covariance structures, and the most appropriate structure was then chosen by selecting the matrix with the maximum Akaike’s information criterion (AIC). The unbalanced covariance matrix structure was determined as the appropriate covariance matrix for this data (BMDP Statistical Software, 1993). The means and standard deviations of cortisol values over the 12-week collection period by groups are presented in Table 9.
Graphs of the cortisol data for the two groups depicted by group by week and group by time are presented in Figure 2 and Figure 3. The cortisol level was found to be different between the exercise and control groups with this difference depending on the week that the level was measured. The graph of group by time illustrates the characteristic peak of cortisol during the morning and the gradual nadir of levels during the evening for both the exercise and control groups.
Figure 2. Individual Salivary Cortisol Levels – Morning and Evening
Figure 3. Overall Mean Cortisol Levels for Exercise and Control Groups. Cortisol levels for exercise and control groups were collapsed into morning and evening timepoints. No significant difference were found between the groups.

In conclusion, there was a significant group by week interaction \((p = .007)\) found between the exercise and control group. Main effects for week and time are not meaningful given the significant second order interaction of group by week. The results of the unbalanced repeated measures ANCOVA for the group of 18 subjects completing the intervention are presented in Table 10. Possible explanations for these findings are discussed in Chapter 5.
<table>
<thead>
<tr>
<th>Interaction</th>
<th>Degrees of Freedom</th>
<th>Chi-Square</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1</td>
<td>1.81</td>
<td>0.178</td>
</tr>
<tr>
<td>Week</td>
<td>5</td>
<td>53.39</td>
<td>0.000</td>
</tr>
<tr>
<td>Time</td>
<td>1</td>
<td>8.61</td>
<td>0.003</td>
</tr>
<tr>
<td>Group by Week</td>
<td>5</td>
<td>15.94</td>
<td>0.007</td>
</tr>
<tr>
<td>Group by Time</td>
<td>1</td>
<td>1.73</td>
<td>0.188</td>
</tr>
<tr>
<td>Group by Week by Time</td>
<td>5</td>
<td>8.08</td>
<td>0.152</td>
</tr>
</tbody>
</table>

Table 10. Results of Unbalanced Repeated Measure Analysis of Covariance on Cortisol Levels between the Exercise and Control Groups

**Summary of Findings**

There were essentially no differences between the completer and noncompleter groups and exercise and control groups on demographic and health variables. This is an important finding in assessing for potential biases between the completer and noncompleter groups, as well as determining if randomization techniques worked in selecting the experimental and control groups. The two research hypotheses that stated the expected relationship between the independent variables and outcome variables were not supported.
CHAPTER 5
SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

This chapter contains a summary and discussion of the findings of this study, their significance, and possible implications for future research. Comparisons with past research are presented where applicable. Conclusions about the effect of exercise on stress state and quality of life in HIV-1 infected individuals are presented.

Summary of the Study

The purpose of this study was to examine the effect of a 12-week aerobic exercise protocol on quality of life and stress in HIV-1 infected adults. Stress state was defined as living with a life threatening disease (HIV/AIDS) that had a potential impact on psychological, physical, spiritual, social, and financial well being (Thompson et al., 1996). For the purposes of this study, quality of life was an individual's perception of well being as reflected by the concepts of physical functioning, role functioning, social functioning, mental health, health perceptions, pain, energy/fatigue, cognitive function, health distress, and overall health.

Since the emergence of the HIV/AIDS over a decade prior to this study, many improvements have been made in drug therapies, resulting in the extension in the lives of
many individuals with this disease. However, with the complex drug regimens and their expense, as well as the adverse side effects, and the long-term adherence needed for therapies, the quality of life for HIV-1 infected individuals may be negatively impacted (Chesney & Folkman, 1994).

It was hypothesized that the use of an aerobic exercise protocol in conjunction with these drug therapies may help to attenuate the harmful psychological, neuroendocrine, and immunological effects of the HIV-1 virus. Therefore, two research hypotheses were formulated for this study: (1) the experimental group, in comparison to the control group, would have improved scores on the MOS-HIV as a measure of quality of life over the 12-week exercise program, and (2) the experimental group, in comparison to the control group, would have significantly lower salivary cortisol levels over the 12-week intervention period.

The theoretical framework used for this study was psychoneuroimmunology, which examined the relationship among psychological variables, the neuroendocrine system, and the immune system. Antoni et al. (1990) proposed an experimental model illustrating the commonly accepted stressor effects on psychological, neuroendocrine, and immunological variables that are relevant in HIV-1 infection. According to this model, stressors (e.g., living with HIV-1) may result in psychological distress, ultimately affecting an individual’s quality of life. An HIV-1 infected individual may experience feelings of social isolation, anxiety, and a loss of control that may serve as the catalyst of psychosocial, neuroendocrine, and immunological events resulting in the acceleration of HIV-1 disease.

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As part of a parent study, an experimental design was used to assess the effect of a 12-week aerobic exercise training program on quality of life and stress state as measured by the MOS-HIV and salivary cortisol levels, respectively. The target population was men and women who were documented to be HIV-1 infected by ELISA and confirmatory Western Blot and meeting other inclusion and exclusion criteria as used in the parent study. Subjects (n = 18) were recruited from the Columbus OH area through publicity from the parent study.

The independent variable for the study was a 12-week aerobic exercise training program. An aerobic exercise training protocol, based on the recommendations of several experts, was that of a three weekly 1-hour sessions, using a stationary cycle ergometer, walking, jogging, or running on a motor driven treadmill. The subjects exercised 60% to 80% of their aerobic power achieved on the GXT pretest.

The two dependent variables in this study were the MOS-HIV (a measure of quality of life) and salivary cortisol (a measure to assess stress state). The MOS-HIV has been documented as a reliable and valid measure of quality of life in HIV-1 infected individuals. The instrument is short, easy to administer, and has been shown to discriminate between individuals with early symptomatic HIV disease and asymptomatic patients (Bozzette et al., 1995; Burgess et al., 1993; Cleary et al., 1993; Wachtel et al., 1992; Wu et al., 1991). Salivary cortisol has been shown to be an inexpensive, non-invasive, valid, and reliable method to measure activation of the HPA axis (Kirschbaum & Hellhammer, 1989; Rolih & Ober, 1995; Vining et al., 1983a). Salivary cortisol, in comparison to serum cortisol, is unaffected by CBG, and thus reflects the biologically
active form of the hormone, suggesting that it is a more appropriate measure of the assessment of adrenal activation.

**Analyses of Completers & Noncompleters and Exercise & Control Subjects**

Non-parametric Mann Whitney U analyses revealed no significant age differences between the completer and noncompleter groups. Fisher’s Exact test analyses determined that there were no differences in education level, race, risk factor, or sex between the completer and noncompleter groups. Statistical analysis using the Mann Whitney U test detected no difference between the completer and noncompleter groups on baseline CD4 and CD8 absolute counts and percentages.

Similarly, non-parametric Mann Whitney U analyses showed no significant age differences between the exercise and control groups. Fisher’s Exact analyses revealed no significant differences in education level, race, risk factor, or sex between the exercise and control group. Also, Mann Whitney U analyses showed no significant differences on CD4 and CD8 absolute counts and percentages, and pretest, posttest, and change scores on the MOS-HIV.

**Salivary Cortisol Analyses in the Exercise and Control Groups**

An unbalanced repeated measures analysis of covariance was used to test for differences in cortisol levels and patterns between the exercise and control groups. A significant “group by week” interaction was found between the exercise and control groups, indicating a difference between groups in cortisol level depending on the week.
that the measurement was taken. Further examination of the data showed that several subjects had markedly higher morning and evening levels of cortisol, compared to other members over the 12-week intervention (Figure 2). These spikes in cortisol may be related to (1) the loss of a family member, (2) prolonged periods of relationship discord, and (3) possible failure of subject to follow protocol for collection of salivary cortisol. Both the primary investigator of the parent study and the investigator of this sub-study were aware of these conditions that may have occurred among several of the study subjects.

Further studies examining the effects of different forms of collection protocols should be investigated, such as having the subject collect saliva in a clinical setting or having the investigator set up specific meetings to monitor saliva collection. In addition, the evaluation of different, more convenient time schedules which are easier for the client to remember, as well as allowing for assessment of diurnal variation, should be investigated.

**Exercise and Lymphocyte Subsets**

No significant differences were found on baseline CD4 and CD8 absolute counts and percentages between the completer and noncompleter groups or the exercise and control subjects. When the remaining five subjects complete the exercise study, further analyses will be conducted to examine pretest to posttest trends between the exercise and control groups.
Exercise and Quality of Life

No significant differences were found between the exercise and control groups on pretest, posttest, and change scores on the MOS-HIV. These findings are in contrast with previous studies. Specifically, research has found that an exercise training program promotes a reduction of anxiety and stress, an increase in feelings of well being, and may help attenuate the destruction of CD4 cells in HIV-1 infected individuals (LaPerriere et al., 1990, 1991; MacArthur et al., 1993; Rigsby et al., 1992). However, the trend found in this sub-study may have a significant impact in developing intervention studies for HIV-1 infected individuals. Further research must be conducted to examine the use of various types of exercise, such as water aerobics, horse back riding, and yoga, which may promote and maintain positive health practices in all stages of HIV disease.

Several rationales may serve as an explanation as to the nonsignificant finding on the MOS-HIV between the exercise and control group. During the 12-week intervention, four of the experimental subjects underwent periods of severe emotional distress, such as death of a family member and relationship discord prior to participation in the study. The incentive of participating in an intervention (exercise) may not have been strong enough to make a difference in the day-to-day lives of these subjects (Dr. Judith Smith, personal communication, August 22, 1997).

Another possibility is that the initial benefits of participating in an exercise intervention may not have been sufficient enough to be reflected in the quality of life measurement. Also, the MOS-HIV has been used as a measure of quality of life in many AIDS clinical drug studies to compare the efficacy of various drug treatments. To date,
there is only one other exercise study using the MOS-HIV at Georgetown University (Dr. Judith Smith, primary investigator). Therefore, the use of the MOS-HIV in assessing quality of life in non-pharmacologic interventions such as exercise is something that merits further study. Quality of life is a very difficult concept to define as well as to measure. More research is necessary using the MOS-HIV to help assess the impact of interventions such as relaxation, touch therapy, and other cognitive behavioral management techniques on quality of life in all spectrums of HIV disease. In addition, other quality of life instruments should be considered for their use in exercise or cognitive behavioral interventions in HIV-1 populations, such as the Visual Analogue Scale, the Health Assessment Questionnaire, or the Quality Audit Marker.

**Exercise and Stress Response**

The finding of a difference in cortisol levels between the exercise and control groups depending on the week which the level was measured is somewhat inconsistent with previous research studies. In studies examining the effects of aerobic exercise on salivary cortisol levels, the intensity and frequency of an exercise protocol had varying results. With chronic submaximal exercise, salivary cortisol decreases. In contrast with acute exercise, salivary cortisol increased (McDowell et al., 1992; O'Connor & Corrigan, 1987).

The specific reasons for the different findings of these studies are unknown. However, McDowell et al. (1992) suggested that differences in the exercise intensity and duration of the aerobic versus anaerobic energy source might be a possible explanation.
More research is needed to examine and replicate the findings of these studies to determine possible mechanisms by which salivary cortisol is decreased through various types of exercise, specifically in chronically ill populations.

The effects of the HIV-1 virus on HPA axis function may be also explain the inconsistent cortisol results. In HIV-1 infection, the mechanisms of the dysregulation of the HPA axis are not clearly understood. It has been suggested that HIV-1 infected monocytes release such factors as IL-1 and interferon (cytokines that has been suggested that to stimulate hypothalamic secretion of CRH). Conversely, adrenal function can be decreased in HIV infection as a result of polyclonal B-cell activation and the production of anti-adrenal cell antibodies. The specific cellular or hormonal determinants and the pathogenetic importance of these antibodies is unknown (Aron, 1989; Grinspoon & Bilezikian, 1992, Verges et al., 1989). More research using techniques such as ACTH stimulation to evaluate the adrenocortical function in HIV positive men will need to be conducted to gain a better understanding as to the HPA modulatory effects on the immune systems in patients with HIV-1 infection.

Conclusion

In conclusion, HIV-1 infection may be viewed as a chronic illness associated with clinical sequelae, such as neoplasias and OIs, which occur during various stages along the disease spectrum. Current PNI research suggests that the use of psychological and physiological stress reduction interventions, such as CBSM, relaxation/hypnosis, and aerobic exercise, may have positive effects on the immune system, quality of life, and
overall health outcomes in HIV-1 individuals. There is a need for continuous research to explore the impact of behavioral and physiological stress reduction interventions across the spectrum of HIV disease.
Appendix A

Heuristic Working Model

Antoni, Schneiderman, Fletcher, Goldstein, Ironson, & LaPerriere, 1990, p. 44.
Heuristic Working Model

A "trial & error" working model for commonly-accepted stress management effects on psycho-social, neuroendocrine/neuropeptide, and immunological endpoints relevant to human immuno-deficiency virus-type 1 (HIV-1) infection. (The symbol (+) indicates increase; (-) denotes decrease.)
Antoni, Schneiderman, Fletcher, Goldstein, Ironson, & LaPerriere, 1990, p. 44.

**STRESS MANAGEMENT**

- Relaxation training/
  Cognitive restructuring
- Anerobic
  exercise

  (+) sense of control
  (+) self-efficacy
  (+) self-esteem

  (-) anxiety, depression, social isolation

  (+) parasympathetic activation
  (-) sympathetic activation
  (-) CRF, ACTH

  (-) peripheral catecholamines and/or cortisol

  (+) B-lipotropin
  (+) B-endorphin
  (+) met-enkephalin

  (-) cAMP/cGMP ratio
  (+) IL-I, IL-II, γ-IFN, MIF

  (+) Ca++ mobilization
  (+) γ-IFN, IL-II, LIF

**IMMUNE ENHANCEMENT**

- (+) Blastogenesis
  (PHA, ConA, PWM)
- (+) CD4/CD8 ratio
- (+) NK cytotoxicity

**DECELERATED HIV-1
DISEASE PROGRESSION?**
Appendix B

Medical Outcomes Survey - HIV (MOS-HIV)

Wu, Rubin, Mathews, Ware, Brysk, Hardy, Bozzette, Spector, & Richman, 1991.
Instructions to the Patient:
Please answer the following questions by placing a "✓" in the appropriate box.

### 1. In general, would you say your health is:

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</table>
- Excellent
- Very Good
- Good
- Fair
- Poor

### 2. How much bodily pain have you generally had during the past 4 weeks?

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</table>
- None
- Very Mild
- Mild
- Moderate
- Severe
- Very Severe

### 3. During the past 4 weeks, how much did pain interfere with your normal work (or your normal activities, including work outside the home & housework)?

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</tbody>
</table>
- Not at all
- A little
- Moderately
- Quite
- Extremely

### 4. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

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<tr>
<td></td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>
- Limited a lot
- Limited a little
- Limited

a. The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running, or participating in strenuous sports.

b. The kinds or amounts of moderate activities you can do, like moving a table, carrying groceries, or bowling.

c. Walking uphill or climbing (a few flights of stairs).

d. Bending, lifting, or stooping.

e. Walking one block.

f. Eating, dressing, bathing, or using the toilet.
For each of the following questions, please check the box for the one answer that comes closest to the way you have been feeling during the past 4 weeks.

<table>
<thead>
<tr>
<th>5. Does your health keep you from working at school, doing work around the house, or going to school?</th>
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<th>6. Have you been unable to do certain kinds or amounts of work, housework, or schoolwork because of your health?</th>
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<tr>
<th>7. How much of the time, during the past 4 weeks, has your health limited your social activities (like visiting with friends or close relatives?)</th>
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<thead>
<tr>
<th>8. How much of the time, during the past 4 weeks:</th>
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<tbody>
<tr>
<td>a. have you been a very nervous person?</td>
</tr>
<tr>
<td>b. Have you felt calm &amp; peaceful?</td>
</tr>
<tr>
<td>c. Have you felt downhearted and blue?</td>
</tr>
<tr>
<td>d. Have you been a happy person?</td>
</tr>
<tr>
<td>e. Have you felt so down in the dumps that nothing could cheer you up?</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
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</tbody>
</table>
For each of the following questions, please check the box for the one answer that comes closest to the way you have been feeling during the past 4 weeks.

<table>
<thead>
<tr>
<th>Check one box in each line</th>
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</table>

9. How often during the past 4 weeks:
   a. Did you feel full of pep?  
   b. Did you feel worn out?  
   c. Did you feel tired?  
   d. Did you have enough energy to do the things you wanted to do?  
   e. Did you feel weighed down by your health problems?  
   f. Were you discouraged by your health problems?  
   g. Did you feel despair over your health problems?  
   h. Were you afraid because of your health?

10. How much of the time, during the past 4 weeks:
    a. Did you have difficulty reasoning and solving problems ... for example, making plans, making decisions, learning new things?  
    b. Did you forget things that happened recently ... for example, where you put things and when you had appointments?  
    c. Did you have trouble keeping your attention on any activity for long? Have you felt downhearted and blue?  
    d. Did you have difficulty doing activities involving concentration and thinking?
11. Please check the box that best describes whether each of the following statements is true or false for you:
   a. I am somewhat ill. □ □ □ □ □
   b. I am as healthy as anybody I know. □ □ □ □ □
   c. My health is excellent. □ □ □ □ □
   d. I have been feeling bad lately. □ □ □ □ □

12. How has the quality of your life been during the past 4 weeks... that is, how have things been going for you?
   □ □ □ □ □
   Very well. Pretty Good & bad Pretty Very bad, could hardly be better about equal be worse

13. How would you rate your physical health and emotional condition how, compared to 4 weeks ago?
   □ □ □ □ □
   Much A little About A little Much better better the same worse worse

Thank you!
Appendix C

Inclusion Criteria
Weight Chart for Men & Women
Metropolitan Life Foundation, 1983.

<table>
<thead>
<tr>
<th>Feet</th>
<th>Inches</th>
<th>Small Frame</th>
<th>Medium Frame</th>
<th>Large Frame</th>
<th>Small Frame</th>
<th>Medium Frame</th>
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<td></td>
<td></td>
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<td>106-118</td>
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<td>101-112</td>
<td>110-123</td>
<td>119-134</td>
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<tr>
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<td>0</td>
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<td></td>
<td>103-115</td>
<td>112-126</td>
<td>122-137</td>
<td></td>
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<tr>
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Appendix D

Instructions for Saliva Collection
Instructions for Saliva Collection

Thank you for your sample in advance!

Here are a few reminders of how to collect your morning and evening saliva samples. Please obtain the “spit sample” between 6:00-7:00 a.m. and then between 5:00 – 6:00 p.m. Please record what time you obtain the sample. I’ll be collecting your samples every two weeks until completion of the study.

1. In the morning, please obtain saliva before taking meds, eating, drinking, brushing your teeth, or smoking a cigarette.

2. Rinse your mouth out with tap water. If there is any blood, rinse a few more times until clear. Wait approximately 5 minutes before you spit.

3. Chew on the rubber band issued to stimulate salivation. Spit into the plastic container and fill until the 5 ml mark. If you can spit more, GREAT!

4. Place your saliva in the refrigerator until Jenise picks the sample up. Will arrange a time with client that is convenient.

If you have any questions, please call Jenise at [__] and leave a message.
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