Clinical Trial of Cognitive-Behavioral Therapy to Reduce Antiretroviral Side Effects in HIV Patients

R. Eric Doerfler

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CLINICAL TRIAL OF COGNITIVE-BEHAVIORAL THERAPY TO REDUCE ANTIRETROVIRAL SIDE EFFECTS IN HIV PATIENTS

A Dissertation
Submitted to the School of Nursing

Duquesne University

In partial fulfillment of the requirements for the degree of Doctor of Philosophy

By
Robert Eric Doerfler

December 2010
CLINICAL TRIAL OF COGNITIVE-BEHAVIORAL THERAPY TO REDUCE ANTIRETROVIRAL SIDE EFFECTS IN HIV PATIENTS

By

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Approved October 13, 2010

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ABSTRACT

CLINICAL TRIAL OF COGNITIVE-BEHAVIORAL THERAPY TO REDUCE ANTIRETROVIRAL SIDE EFFECTS IN HIV PATIENTS

By

R. Eric Doerfler

December 2010

Dissertation supervised by Linda Goodfellow, PhD, RN

Antiretroviral therapy (ART) for HIV/AIDS has led to significant improvements in survival and a reduction in AIDS-related morbidity. Adherence to regimens is vital, yet clinical observations and research have suggested that side effects are a significant reason for non-adherence. This randomized, controlled clinical trial was a pilot study sought to determine if a brief exposure cognitive-behavioral therapy (CBT) could reduce side effect symptoms in HIV/AIDS patients on ART. Methods: 33 participants were randomized to standard adherence education alone or adherence education plus three sessions of CBT over a period of three months. Results: Completing the study were 17 males and one female; whites, blacks, and Hispanics were represented in the sample. Mean duration of ART was over 200 weeks. Participants in the experimental group reported significantly less nausea and fatigue, compared to those in the control group (Mann-Whitney U, p <
.05). There were no differences in adherence across the study, which was reported at >94%. No differences in CD4 lymphocyte counts or viral load were observed between groups over the course of the study. Observations suggested that scheduling visits with the psychologist delivering the CBT sessions was an obstacle to continued participation. The use of side effect reducing medication was low in both groups. Increasing daily practice sessions was correlated with an increase in reported nausea scores. The reason for this observation is not known. Brief exposure to CBT training in male HIV/AIDS patients on ART appears to reduce side effect symptoms. A larger sample with more female representation is warranted to further explore this intervention Referral for CBT to reduce side effect symptoms in similar patients may be warranted.
DEDICATION

This research is dedicated to the late poet Stephen R. Norris, and to my wife, Julie Moffitt, for her patience and support during the process.
ACKNOWLEDGEMENTS

I would like to acknowledge Dr. John Zurlo, Nurse Daphne Greenawalt, and the rest of the Caring Together team, the patients who participated in this study, as well as the staff at the Infectious Disease Clinic at the Penn State Milton S. Hershey Medical Center, for their assistance in making this research possible. Funding for this study was provided by Penn State Harrisburg and the Beta Sigma Chapter of Sigma Theta Tau Nursing Honor Society (Penn State School of Nursing, State College, PA). Special thanks to Cinda Boyer (Special Hematology Lab) and Nate Sheaffer (Cell Science Core Facility) at the Penn State Milton S. Hershey Medical Center for their technical assistance. Thanks to Dr. Kathrine Bakke-Friedland for her assistance during independent study for project planning and intervention design, and to Paul Ricci for statistical consultation. Thanks to the Penn State School of Nursing and Dr. Mary Beth Clark for providing facilities for the behavioral intervention. Finally I would like to acknowledge my Dissertation Committee, Drs. Linda Goodfellow and Mary Ann Thurkettle of Duquesne University, and Dr. Suzanne Willard of the Elizabeth Glaser Pediatric AIDS Foundation, for their guidance, tireless work, and assistance with this project.
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Chapter 1

Statement of the Problem

Introduction

Side effects can occur from the use of any drug. Patients who have human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) related to HIV follow a similar course of treatment similar to that of the cancer patient undergoing chemotherapy. As with all medicines, antiretroviral treatment (ART) for HIV/AIDS may result in side effects that limit patients’ ability to continue treatment. Clinically, the researcher has listened to HIV/AIDS patients on ART describe feeling “toxic” or “sick on the meds.”

Those with HIV who are on ART may miss medication doses or discontinue the regimen for various reasons. Reasons for non-adherence include substance abuse, forgetfulness, scheduling difficulties and lifestyle interference, and misconceptions about the use of the elements of ART. A significant reason for discontinuation is side effects, including side effects not responsive or only partially responsive to anti-side effect medications (Bartlett, 2002; Chesney, 2000, 2003; Laws, Wilson, Bowser, & Kerr, 2000). An anecdotal observation is that despite treatment with side effect reducing medications (SERM) some patients’ symptoms grow worse. Patients on ART have made statements such as, “I know this is all in my head.” Thus, some patients seem to understand that their own mental framing of ART can influence their experience of side effects. Based on oncology literature the author referred a few such patients to a cognitive-behavioral therapist for help controlling side effects and anxiety. The researcher’s request at the time was for the therapist to provide cognitive-behavioral therapy (CBT) to help those patients reframe the experience of ART and
to teach them techniques for reducing anxiety and emotional arousal associated with that experience. In this very small series of patients, two went on to successful ART with moderated side effects and an improved ability to sustain adherence to their regimens over time. This clinical anecdotal experience, in addition to studies reported in the oncology and psychological literature, are the bases for this study.

Questions

The present study examined whether CBT can help to reduce the discomfort of side effects in ART. It was hypothesized that a reduction of side effects might alter how patients adhere to their regimens. Finally, it was further hypothesized that if patients adhere better, there might be changes in serum levels of HIV, and CD4 lymphocyte counts. This led to the following questions for study:

- Will a CBT intervention reduce side effects (nausea, pain, fatigue, and/or anxiety) in HIV patients undergoing ART compared to patients who only receive education on proper adherence to medication (standard of care [SOC])?
- What is the relationship between measured side effects and self-reported adherence?
- What is the relationship between measured side effects and clinical measures (CD4+ lymphocyte [CD4] counts and serum viral burden [“viral load,” VL])?

Hypotheses

- Participants who receive the CBT intervention will report a reduction in side effects, compared to participants who only receive the SOC.
- Participants who receive the CBT intervention will show a difference in adherence compared to those who only receive the SOC.
Participants who receive the CBT intervention will show a difference in CD4 and VL compared to those who only receive the SOC.

Assumptions Underlying the Research

Methodological assumptions underlying the research were:

- Study participants were honest in their symptom reporting, as well as how they felt mentally and physically.
- Participants were able to make reliable estimates of symptom intensity and duration, and faithfully marked the instruments thus. It was assumed that participants would not hurry through the questions, nor hastily mark answers in order to “get through” the questions quickly.
- Laboratory data from various laboratories is standardized. A detailed discussion of laboratory methods and standardization appears in Chapter 3.

Definition of Terms

Adherence. Patients’ ability to continue on a medication or other treatment regimen is generally subsumed under the rubric of “compliance” or its more recent phrasing “adherence.” Alternative ways of defining compliance recognize patient participation in clinical decisions, with clinicians serving as expert advisers (Vermeire, Hearnshaw, Van Royen, & Denekens, 2001), and “adherence” has become popular (Dunbar, 1980; Lieberman, 1996). The terms are often used interchangeably, but adherence is the term of choice among treatment professionals in HIV disease. Adherence in this study was measured as the percentage of doses taken, according to the regimen, based on patient recall, recorded on the VAS and proportion of doses taken in three days, a measurement known as “three-day recall”. The use of VAS in adherence measurement in HIV is discussed under methodology.
Antiretroviral therapy. Antiretroviral therapy is the use of a minimum of two antiretroviral drugs with the aim of reducing serum viral nucleic acids below the limits of detection. Most commonly, at least three agents from at least two different classes of antiretroviral drugs form the basis for any regimen (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2009).

Clinical endpoints. Clinical Endpoints were measured by CD4+ lymphocyte subset (“CD4 count”) and serum HIV nucleic acids (“viral load”) which are the standard measures, termed clinical endpoints, in HIV/AIDS treatment centers (Fahey et al., 1990). CD4 count and viral load were measured at two time points, at the beginning and at the end of subject participation in the study. Only results from samples within 30 days of the beginning of the study (first measurement) or end of the study (last measurement) were used.

Cognitive-behavioral therapy (CBT). In this study, CBT is defined as a system of psychological treatment based on the understanding of a patient’s beliefs and thoughts, which drive their experience. In CBT theory, so-called automatic thinking contributes to discomfort or psychological distress. In CBT the patient’s thoughts are reframed through discussion and education. Adjunctive techniques to reduce arousal aid this process. Such techniques include relaxation, guided imagery, biofeedback, and other methods (A. T. Beck, 1976).

Side effect symptoms. In this study there are two types of symptoms to consider. The first type of symptom signals some potentially serious problem such as anemia, lactic acidosis, or peripheral neuropathy. The second type of symptom includes sensations that are bothersome, but do not necessarily demand a change of regimen or other medical intervention. Several of the symptoms that this study examined fit into both categories. Serious problems were ruled out by the usual clinical follow up, just as in normal practice.
Once serious problems were ruled out, what remained were the persistent, troublesome, wearying symptoms that were the focus of this study: nausea, fatigue, pain, and anxiety. The terms *discomfort* and *comfort* are defined as the presence or absence of those four symptoms, and are also related to the domain scores of the Short Form-36 (SF-36).

**Nausea.** Nausea is defined as an unpleasant sensation localized to the abdomen. In vernacular terms it is also described as “queasiness,” or being “sick in the stomach” (NCCN, 2005). The perception of duration of nausea, its average perceived intensity, and its greatest perceived intensity were measured by VAS at four time points.

**Pain.** In this study, pain is an unpleasant sensation rooted in nociception that may or may not be related to tissue damage (Joffe & Sandler, 1967; Merskey & Spear, 1967). Pain may be malignant or non-malignant, and other than ruling out life threatening causes, the cause of the pain was not considered. The perception of duration of pain, its average perceived intensity, and its greatest perceived intensity were measured by VAS at four time points. Pain over the last four weeks was also be measured by verbal intensity scaling (Item 7) in the Short Form-36, at four time points.

**Fatigue.** Hart, Freel, and Milde (1990) defined fatigue as “a subjective self-evaluation of sensations associated with discomfort, decreased motor and mental skill and increased task aversion” (pp.967-968). Tack (1990), looking at fatigue reported by rheumatoid arthritis patients described it as, “the subjective sensation of generalised tiredness or exhaustion” (p. 154). The perception of duration of fatigue, its average perceived intensity, and its greatest perceived intensity was measured by VAS at four time points. Role performance (RP), physical functioning (PF), and vitality, terms operationalized in the SF-36, was also measured as behaviors (RP and PF) and sensation (vitality) related to fatigue, at four time points.
Anxiety. Whitney (1992) defined anxiety by four critical attributes.

- There is the presence of a vague, uneasy feeling of discomfort or dread.
- The source or cause of the anxiety is unknown or nonspecific in origin.
- Subjective responses that act as energizers (i.e., prompt action) but cannot be observed directly are present; these responses may be classified as psychological/behavioral.
- Objective signs that are the result of the transformation of the energy into relief behaviors are present; these signs may be classified as physiologic, psychological/behavioral, or cognitive.

The perception of duration of anxiety, its average perceived intensity, and its greatest perceived intensity was measured by VAS at four time points. Role-emotional (RE), social functioning (SF), and mental health (MH), terms operationalized in the SF-36, were also measured as related to anxiety, at four time points. However, domains such as MH also include measurement of items related to depression and other aspects of mood. This is considered further in Chapter 5.

Theoretical Framework

The theoretical framework for this study was based on cognitive control of autonomic responses. Skinner (1971) suggested the use of consequences to modify behavior (operant conditioning), but Pavlov’s original work dealt with classical, also called respondent, conditioning. Respondent conditioning is reflexive, intimately coordinated with the sympathetic and parasympathetic branches and endocrine function, and targets physical responses operated by those systems, chiefly as a means of ensuring that organisms adapt to their environment (Rescorla, 2003). Pavlov’s classic example was based on the fact that the
presentation of food leads to saliva production. The dog in Pavlov’s experiment was given food when a bell was rung. The stimulus of the bell was paired with the stimulus of being given food, and an autonomic response was generated.

Anticipatory nausea and vomiting (ANV) in antineoplastic therapy is one example from oncology that exemplifies how conditioning combined with autonomic arousal potentiates symptom experience. The nausea and vomiting that may have occurred from a first chemotherapy treatment form a stimulus-response pair. The circumstances of the event become paired with nausea and vomiting and may elicit the autonomic response without actual antineoplastic therapy being administered. A similar-appearing process has been observed by the author to occur in patients on ART. In their theoretical analysis of ANV, Burish and Carey (1986) noted that there are several theories about how this problem develops. Proposed alternative theories with, they argue, less supporting evidence are 1) psychodynamic readjustment to serious illness, 2) attention-seeking behavior, and 3) anxiety-induced nausea related to as-yet-poorly understood mechanisms in brain and gut tissue. Respondent conditioning is essentially classical conditioning, but Burish and Carey note that even this generally-accepted theory fails to explain why some people develop conditioned responses and others do not, nor why varying numbers of exposures to adverse symptoms lead to the conditioned responses in different patients (lending some credence to the possibility of alternate explanations). The authors posit an extension of the respondent conditioning theory, that such conditioning is mediated by anxiety.

In this way, the theory selection for this project admits that ART may be a desired option, indeed may be understood as necessary and life-saving by the patient. However, the emotional reaction to that experience may change patient reactions even though he/she knows
such reactions may reduce his or her ability to maintain the treatment. Thus, the theory suggests that strategies to reduce anxiety as well as change automatic thinking would be beneficial.

Burish and Carey (1986) propose that anxiety is a key mediating factor in somatic symptoms such as ANV and other complaints. From the theoretical perspective in this study, CBT offers a means to address several factors at once.

Cognitive-behavioral therapy proposes that life challenges may be engaged by discovering the complaint (e.g., “I’m anxious about taking my meds.”) and then to determine what maladaptive automatic thinking drives that emotional sensation (A. T. Beck, 1976; J. S. Beck, 1995). The goal of CBT is to engage higher cortical function to change the automatic thinking, which relieves the emotional sensation. Behavioral techniques serve to gain autonomic control (which can also serve to shift the locus of control inward), which in turn makes it easier for the patient to assert control over automatic thinking (A. T. Beck, 1976; J. S. Beck, 1995; Kalichman, 1995).

**Significance to Nursing**

Schieterger and Daniels (1996) interviewed HIV/AIDS patients on their perceptions regarding their health care, and in particular, how they view their health care providers. Of the five themes that emerged, one pertinent to the aim of this study is that patients wanted their providers to appreciate them holistically, that is with a sense of the importance of their psychosocial and spiritual needs, as well as the physical needs. Nurses assess patients for potential problems with side effects and adherence (Spirig, Moody, Battegay, & DeGeest, 2005; Wolfe, 1997). Taking a diagnostic approach (Caetano & Pagliuca, 2006), HIV/AIDS patients who undertake ART are at risk for the diagnoses in Table 1.1
Table 1.1

Common Nursing Diagnoses Applicable to Patients on ART

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<td>Activity alteration</td>
</tr>
<tr>
<td>Activity intolerance/risk</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Body nutrition deficit/risk (related to nausea/vomiting)</td>
</tr>
<tr>
<td>Chronic pain</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Fluid volume deficit/risk</td>
</tr>
<tr>
<td>Instrumental Activities of Daily Living (IADLs) alteration</td>
</tr>
<tr>
<td>Knowledge deficit of therapeutic regimen</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Sleep pattern disturbance</td>
</tr>
<tr>
<td>Swallowing impairment (related to anxiety, with impact on dose consumption)</td>
</tr>
<tr>
<td>Unspecified pain</td>
</tr>
</tbody>
</table>

The diagnoses in the Table focus on problems related to ART. The Table also does not include diagnoses that are *unlikely* to respond to cognitive-behavioral interventions as designed in this study (e.g., progressive muscle relaxation, guided imagery), such as diarrhea and/or bowel incontinence, blood pressure alteration and/or respiration alteration. Examples of this include anemia due to non-nucleoside reverse transcriptase inhibitors (NRTIs), contraceptive risk related to pregnancy that may occur during occurring during use of efavirenz [Sustiva®, Bristol-Myers Squibb, New York]), or tactile alteration from sensory loss related to neurotoxic agents such as stauvudine [Zerit®, Bristol-Myers Squibb, New York]).

Pharmacologic therapy of HIV/AIDS has become the mainstay of medical treatment. Nursing complements such treatment in several ways. This study concerned itself with a possible method nurses may use to complement medical therapy, by helping patients remain adherent through the employment of a method which may reduce side effect burden.
Summary

This study was a randomized, controlled clinical trial that compared the use of CBT/SOC to SOC alone in an attempt to reduce side effect symptoms in HIV/AIDS patients on ART. The study also sought to explore whether symptom reductions led to improvements in adherence to medical regimens, and further, to greater improvements in CD4 counts and viral loads, compared to controls. Standard of care was defined as adherence education and side effect monitoring, as currently practiced. Nausea, pain, fatigue, and anxiety as measured by VAS at four time points in this multiple measures study, were the main dependent variables. Anxiety may potentiate the other three symptoms, as well as serve as a source of discomfort itself. The theoretical framework of the study is based on cognitive control of autonomic responses. Theory suggests that symptoms such as the four selected for this study would respond to a reduction in autonomic arousal. Cognitive therapy and behavioral techniques are one means by which patients may access control of arousal, thus leading to a perceived reduction of the symptoms under study, and the use of CBT was the independent variable in the study. Nurses diagnose the symptoms suffered by HIV/AIDS patients on ART and intervene to reduce those symptoms. The study explored the utility of a method by which nurses may improve the care and comfort of their patients.
Chapter 2

Review of the Literature

The Three Historical Periods of HIV Management

Clinical HIV disease was detected when several homosexual men, who had no known cause of immunodeficiency, were treated for pneumonia caused by *Pneumocystis carinii* (now *P. jirovecii*), an opportunistic pathogen that only causes disease in the immunosuppressed, in 1981; two died (CDC MMWR, 1981). From the beginning an epidemiological pattern suggested an infectious cause was among the hypotheses for this acquired immunodeficiency, although there were also many competing hypotheses including immunodeficiency induced by abused inhalants such as amyl nitrite, or autoimmunity stemming from exposure to spermatozoa. By 1985 the cause of AIDS was elucidated at about the same moment in both France and the United States (Sepkowitz, 2001). Disease-causing retroviruses were not entirely new. The observation that certain RNA viruses (in which the genome is carried in ribonucleic acid, analogous to a photographic “negative”) copied their genetic information into host-cell DNA (deoxyribonucleic acid) changed the way biologists had always thought about the direction of genetic information transfer (classically, from DNA to RNA to protein) (Fauci & Longo, 2001). Since then HIV has infected tens of millions throughout the world (Sepkowitz, 2001; UNAIDS, 2006). During the more than 20 years of the AIDS epidemic, there have been three phases. The first, from 1981 to 1985, involved elucidating the cause. The second, from 1985 to 1996, was a period in which all attempts at therapeutic success against the virus led to failure, and the infection was considered fatal. The third period is from 1996 to today, the age of effective combination ART. However, this has not led to the hoped-for “cure” of HIV infection *per se*. In the next
sections, this and related issues will be discussed in terms of the life cycle of HIV, its affinity for key immune system component cell types, its viral dynamics and genetic instability, why treatment must endure for long periods of time, and how viral genetics may lead to drug resistance when patients are unable to adhere to the regimens properly.

Immunobiology of HIV

Retrovirus Genetics and the Persistence of HIV Infection. As suggested above, retroviruses become a part of the host cell genome. Thus, elimination of an HIV infection must also eliminate every infected cell in the host. A detailed discussion of the gene sequences in retroviruses is beyond the scope of this paper, but it is important to note one feature. This involves the first step in the productive infection of host cells by retroviruses, as well as the formation of antigen-specific immune competence.

Normal Human Immune Responses. Cluster of differentiation (CD) is a set of over 250 cell surface antigens that act as receptors, ligands, and perform other tasks. The fourth in the series, CD4, is a 55 kiloDalton protein chain occurring on certain thymocytes, macrophages, and lymphocytes. Major histocompatibility complex (MHC; types I and II) on host cells contains a small sample of viral peptide which has been derived from within the infected host cell to form a supercomplex that comes into contact with a T-cell receptor (TCR). The signal that results from this sequence of events triggers the CD4 lymphocyte to activate macrophage killing of bacteria, and B-lymphocytes to differentiate and produce antigen-specific immunoglobulins. Macrophages are a major cell subset in immunity to bacterial infection. Immunoglobulins help to provide immunity to viral infections and to neutralize bacterial and other toxins (Janeway, Travers, Walport, & Shlomchik, 2005).
Retroviruses Downregulate Normal Human Immunity. The lentivirus family of retroviruses, and especially HIV, contain a coding sequence, nef (negative-regulation factor), which downregulates CD4, and since this is a key component of the MHC/TCR complex and serves as the cellular receptor for HIV, T-lymphocyte activation pathways are altered, affecting immune system function downstream (Fauci & Longo, 2001; Janeway, et al., 2005).

HIV. An encapsulated virus approximately 100nm in diameter, HIV contains a 9.7 kilobase (kb) genome consisting of three major structural genes, including the reverse transcriptase (RT) gene—the gene that makes a retrovirus what it is, enabling HIV to “write itself into” the genes of host cells for which it is tropic (Streicher, Reitz, & Gallo, 2000).

The virus fuses with the host cell via the gp120/gp41 complex on its lipid membrane; the complex itself binds with CD4. For entry, the virus uses one of two co-receptors located on cell membranes, CCR5 (on T-cells, macrophages and microglia) (Choe et al., 1996; He et al., 1997; Lederman, Penn-Nicholson, Cho, & Mosier, 2006) and CXCR4 (on T-cells) (Berger, Murphy, & Farber, 1999). Small changes in the V3 loop of gp120 direct whether a particular strain will target CCR5 or CXCR4 receptor types.

Following fusion, the virus core enters the cytosol, at which time free viral RT enables incorporation of the viral genome into host cell DNA (integration). T-cell activation seems to be required for viral disassembly and the fusion of additional viral particles (Cleghorn, Reitz, Popovic, & Gallo, 2005; Gowda, Stein, Mohagheghpour, Benike, & Engleman, 1989). Viral positive-stranded RNA is transcribed into nuclear DNA—even in resting cells, and it is believed that this is one of the means by which HIV reservoirs may remain stable for extremely long periods (years or even decades) in resting T-lymphocytes, monocytes, and macrophages (Cleghorn, et al., 2005).
Later, when cells undergo division, as in response to clonal expansion following an infection to which CD4+ lymphocytes respond, virus is produced as well, using host cell regulating enzymes (transcription) (Streicher, et al., 2000). However, active cell division is not required, as viral production occurs even when cells are not actively mitotic (Graziosi et al., 1993). After new viral proteins are generated, viral proteases cleave the new strand of protein, and other enzymes assemble the virus for budding from the cell surface (Streicher, et al., 2000). Figure 2.3 depicts the life cycle of HIV and displays multiple drug targets at the fusion, reverse transcription, integration and protease production stages.

**Figure 2.1** Life cycle of HIV.

**Figure 2.3.** Antiretrovirals target binding, fusion, reverse transcription, proviral integration, and early assembly. From Cleghorn, Reitz, Popovic, and Gallo (2005).
Ho et al. (1995) showed that daily HIV production is quite high. Perelson, Neumann, Markowitz, Leonard, and Ho (1996) found that replication proceeds on the order of \(10.3 \times 10^9\) virions/day. Richman et al. (2004) demonstrated that an average of one mutation during each replication of each genome occurs. Mathematical models of HIV replicative error rates suggest that each day, every possible mutation—including drug resistance mutations—can occur at least once, and many may occur several times (Coffin, 1995; Perelson, et al., 1996). It is believed that retroviruses gain survival advantages from this high rate of error, enabling the frequent appearance of drug-resistance mutations, as well as a rapid rate of replication to create large numbers of viral particles (Mansky, 1998; Richman, et al., 2004).

**Immunological Events in HIV Infection**

**Early infection.** The development of HIV infection begins with inoculation across broken skin or upon mucosa, usually rectal or vaginal in humans. Here tissue- or mucosa-resident dendritic cells (DCs) acquire contact with the virus and transport particles to nearby lymphoid tissue, chiefly nodal tissue, where T-cell infection is thought to take place in DC/T-cell complexes that are a normal part of the immune response. Evidence suggests that the DCs are not actively infected, although such cells do express low levels of CD4. It is believed that the proximity of the T-cells to active virus on the surfaces of DCs leads to the initial introduction of HIV into host cells for virus production (Dybul, Connors, & Fauci, 2005).

At this stage, serum viral burden may reach \(10^7\) virions/mL and may cause acute retrovirus syndrome, a constellation of symptoms resembling influenza or mononucleosis, as nonspecific innate mechanisms and cytokines such as interferons are secreted by an activated immune system (Perelson, et al., 1996; Perlmutter, Glaser, & Oyugi, 1999; Streicher, et al., 2000). The first antibodies to HIV appear within two weeks in some individuals, but may not
be detectable by typical commercial antibody assays until six weeks into infection. Early stage neutralizing antibodies exert no control on the rise of viral burden, with stronger humoral responses, supported by antibody-bound complement, and activated cytotoxic lymphocytes (CTL, CD8+ lymphocytes) developing in 10-21 days to begin to bring the infection under control. The rise of this later, complement-binding antibody does seem to control viral spread (Pantaleo & Fauci, 1996).

**Chronic Infection.** As serum viral burden decreases in response to the now-invigorated and specific CTL response, two sources of persisting HIV are believed to be responsible for latent reservoirs of infection: proviral DNA woven into resting T-helper cells and follicular dendritic cells (FDCs) in peripheral lymphoid tissue (Pantaleo & Fauci, 1996). As was noted earlier, retroviruses copy their own genetic code into host target cell DNA strands. T-helper cells (THCs, CD4+ lymphocytes) are part of a pool of cells that assist thymic-dependent antibody responses by interacting with MHC-II/antigen complexes on B-lymphocytes. Such helper cells also activate macrophages, assist CTL killing of virus-infected cells by inducing proliferation of those cells, and induce cytokine production in response to infection. A pool of resting THCs may be “naïve,” specific antigen-ready and unarmed, or they may instead be “memory” cells, with matured antigen specificity and primed for rapid clonal expansion upon new contact with the “memorized” antigen (Figure 2.4).

In either event, these lymphocytes are critical to initiating adaptive responses to new pathogens ( naïve cells) and initiating rapid responses (with correspondingly lower energy costs) to previously-presented pathogen antigen (memory cells). The maintenance of the
memory pool of THCs in particular sustains immune system competence and antigenic memory over decades (Janeway, et al., 2005).

If it is the quality of the immune response and (Pantaleo et al., 1997) and the number of T-lymphocytes and other immune cells (Pantaleo & Fauci, 1996; Pantaleo, Graziosi, & Fauci, 1993) that together determine the level of sustained viremia in HIV patients, it is the persistence of the pool of resting CD4 cells, assisted by constant low-level stimulation from FDCs, that forestalls apoptosis, and maintains the infection itself. It has been shown that the deterioration of the CD4 lymphocyte pool may not even be due to direct killing by virus. Indeed HIV maintains T-cells as productive virus factories. Rather it may be immune activation (Sousa, Carneiro, Meier-Schellersheim, Grossman, & Victorino, 2002) and robust
CTL that depletes the host’s immunity and eventually leads to clinical symptoms (Borrow, Lewicki, Hahn, Shaw, & Oldstone, 1994; McMichael & Rowland-Jones, 2001). The clinical events that do result from diminution of the CD4+ lymphocyte pool is discussed further below.

**Late clinical events.** Whatever the ultimate cause of the depletion of THCs, over a period of 18 months to 10 years, most untreated persons will develop some evidence of clinical disease (Mellors et al., 1997). There is ample evidence to suggest that genetic, immunologic, and possibly viral causes exist for both rapid, early disease, and non-progression to clinical AIDS (Berger, et al., 1999; Cao, Qin, Zhang, Safrin, & Ho, 1995; Graziosi, et al., 1993; Haynes, Pantaleo, & Fauci, 1996; Pantaleo, et al., 1993; Wei et al., 1995). Although it has been suggested that clinical progression in HIV disease may be a result of immune activation or immune dysregulation, opportunistic infection remains a significant cause of morbidity and mortality. Major primary causes of death worldwide from HIV include tuberculosis and Streptococcal pneumonia. Other causes are cervical neoplasia, lymphoma, and other cancers, especially those associated with certain viral infections, such as Kaposi’s sarcoma (associated with herpes simplex 8 infection) (Roizman, 1995). Thus, whatever factors cause sickness in HIV-infected patients pharmacologic suppression of virus remains the mainstay of treatment. This fact provides the impetus for this proposed study: If drug therapy matters, and if adherence matters, then means to maintain that adherence matter to nurses who treat HIV/AIDS patients.

**Antiretroviral Therapy and its Implications: The Bases for ART Today**

Zidovudine (ZDV) is a thymidine analogue that was found to be efficacious in the inhibition of the integration phase, though its blocking of reverse transcriptase at the coding
target (Furman et al., 1986; Parks et al., 1988; Shiau, Schinazi, Chen, & Prusoff, 1980; Uherova, Schmidtmayerova, & Mayer, 1991). Ultimately, single-agent therapy did not reduce significantly longer term mortality in AIDS patients, and there was evidence that the virus was becoming resistant to ZDV and that toxicity limited treatment tolerance (Rachlis, 1990). Zidovudine did not significantly alter the course of the disease (Volberding et al., 1994), and single class regimens of several nucleoside analogues were not any more successful (HIV Trialists Collaborative Group, 1999), and could be antagonistic (Havlir et al., 2000).

In the mid-1990s multi-drug therapy studies in parallel with the development of polymerase chain reaction (PCR) techniques that allowed direct measurement of virus in serum, led to the conclusion that multiclass ART could hold the key to more durable effective treatment (Collier, Coombs, Schoenfeld, Bassett, Baruch, et al., 1996; Collier, Coombs, Schoenfeld, Bassett, Timpone, et al., 1996; Danner et al., 1995; Eron et al., 1995). A multi-center cohort study by Mellors, et al. (1997), showed that prognosis varied proportionally to viral load and inversely with CD4 counts. This seemed to suggest that durable, constant suppression of virus could forestall immune decline from HIV infection. These studies seemed to suggest that saving HIV patients could be accomplished through attacking the life cycle at two or more points (Gulick et al., 1998; Gulick et al., 1997; Hammer et al., 1996; Hammer et al., 1997; Palella et al., 1997). Recent data demonstrate that potency alone may not be enough to control HIV, as “triple nucleoside” regimens proved inadequate to provide long term control for patients with serum viral loads above 100,000 copies/mL (Gulick et al., 2004). Inhibitors of the RT enzyme itself (as opposed to inhibition of its substrates, e.g., thymidine), inhibitors of protease, and more recently, inhibitors of fusion have been combined with nucleoside RT inhibitors, such as ZDV, to create effective
multiclass ART (Palella, et al., 1997; Panel on Antiretroviral Guidelines for Adult and Adolescents, 2006; Sepkowitz, 2001).

**Antiretroviral Resistance and Adherence**

The dynamics of HIV, the consequence of unchecked infection, and the effectiveness of multiclass ART were explained in previous sections. To summarize: HIV “writes itself” into the genetic code of host cells, chiefly CD4+ lymphocytes and macrophages. Viral elimination may not be possible: resting memory T-cells may harbor proviral DNA for decades, sequestered from the action of available drug therapy (Finzi et al., 1999). Replication proceeds with many errors, yielding inactive virus, but also yielding some adaptive mutations. Thus, the cornerstone of ART now is the creation of regimens that effectively shut down viral replication. If there is no replication, there can be little to no opportunity for the creation of drug resistance mutations (Patel & Patel, 2006).

Viral replication commences relatively soon after serum drug levels fall below their inhibitory concentrations (Blaise, Clevenbergh, Vaira, Moutschen, & Dellamonica, 2002; Tobin et al., 2005). The goal of ART is to maintain constant, therapeutic drug levels. Missing doses may lead to drug levels falling below those levels. There are many reasons for non-adherence, including patient preference or competing life goals, various behavioral or psychological impediments such as substances abuse or low self-esteem, and socio-economic problems to include changing residence jurisdiction (e.g., for patients on public assistance), and so forth (Benedetto, 2003; Chesney, 2000; Marhefka, 2002; Ramirez & Cote, 2003). The present study was concerned with non-adherence related to unpleasant side effect symptoms, whether they are from the actions of the drugs or from psychosomatic effects, such as nocebo or context effects.
Variations in adherence have been characterized based on dosing frequency alone (Mannheimer, Friedland, Matts, Child, & Chesney, 2002) and dosing frequency versus dose timing (Ferguson et al., 2005), with the former having been better studied. An ideal adherence level of >90% of doses taken is associated with durable viral suppression (Robert Gross et al., 2006; Lowe, Prins, & Lange, 2004; Press, Tyndall, Wood, Hogg, & Montaner, 2002). The high rate of replicative error combined with loss of viral suppression leads to the emergence of viral resistance (De Olalla et al., 2002; Rouzine & Coffin, 2005).

Thus, the goal of ART is to suppress virus and spare the immune system both CD4 T cell depletion and excessive chronic activation. Clinical deterioration has been shown to correlate well with levels of CD4+ lymphocytes (Fahey, et al., 1990). Suppression of virus leads to a restoration of certain immune cell subsets, and has been shown to thus lead to immune reconstitution and clinical improvement (Hung & Chang, 2004). If patients cannot adhere because of side effects, or suffer too long from feeling ill on ART, adherence can suffer, and this can lead to loss of suppression outright (when medications are halted) and/or drug resistance (when medications are taken correctly less than 90% of the time) (Press, et al., 2002; Rouzine & Coffin, 2005).

Summary

Infection with HIV is persistent, and at present permanent, due to the unique way that retroviruses become part of the host cell genome. Infection is highly dynamic and results in significant immune system activation. Infection also targets specific human immune cell types that lead to weakening of immunity, and opportunistic infection is a late and often fatal result. Persistence of the virus owes to persistence of very specific THC subsets that are long-
lived. Although virus may be suppressed for years, small numbers of resting THCs are 

enough to seed a full-scale reinfection if drug pressure is removed.

The dynamics of HIV result in many mutations, and drug resistance mutations are a 
daily occurrence, but competition with wild-type virus limits its persistence in the host. Drug 
pressure suppresses viral replication and also limits the emergence of drug resistance.

Intermittent use of ART or the use of incomplete regimens lead to incomplete suppression,
and drug resistant variants emerge. These variants lead to viremia despite therapy, and the 
clinical consequences of unchecked HIV infection can resume. The effectiveness of entire 
classes of antiretroviral drugs can be lost.

For these reasons, ART is currently considered a lifelong therapeutic enterprise. 

Interruptions are not usually catastrophic, but can only be short-lived in most patients.

Reasons for interruption include drug toxicity. Otherwise, patients must remain on ART 
continuously. Minimizing side effect symptoms assists the goal of adherence, and continuous 
adherence is, for now, the only effective long term treatment strategy in HIV disease.

**Educating Patients for Adherence to Antiretroviral Therapy**

From early in the era of ART it was observed that failure to adhere to medications 
properly can lead to drug resistance (Bangsberg, 2006; Bangsberg et al., 2000; Blaise, et al., 2002; Tobin, et al., 2005), that this can lead to poor clinical outcomes (De Olalla, et al., 2002; Press, et al., 2002; Richman, 1994), and thus requires diligent efforts toward improving 
patient adherence to the regimens as prescribed (Esch & Frank, 2001). “Adherence 
education” or “adherence training” are terms that have arisen in the clinical vernacular of 
HIV specialist clinicians whose patients often expect to actively participate in their care
choices, an outcome of the activist politics surrounding the HIV epidemic. This raises the question: In HIV treatment, what is adherence education?

Teaching patients how to utilize a prescribed regimen is probably one of the oldest interventions in human history, and Hippocrates referred to patients who did not take their medications for various reasons (Vermeire, et al., 2001). It is beyond the scope of this project to review everything known about teaching patients how to use their medications. However, establishing that regimens are complex, that failure to take the regimens properly can have serious consequences, and that therefore adherence has special significance in ART calls for a discussion of adherence as it applies to ART. It is also important to note that reviews of “patient compliance” tend to devolve to a few issues. Patients choose to adhere to medical regimens when the expected gain exceeds the perceived losses—in time and inconvenience, in suffering due to side effects, in their sense of social stigma (especially pertinent in disease like HIV/AIDS) (C. Golin, Isasi, Bontempi, & Eng, 2002; Wilson, Hutchinson, & Holzemer, 2002). Also important is that patients believe that their concerns about treatment have been heard and have formed part of the plan (Dunbar, 1980; Lieberman, 1996). Yet as Chesney (2003) notes, substance abuse, domestic violence, transience of habitation, loss of insurance and other issues have significance as well. These issues could be subsumed under the rubric “readiness to therapy.” But readiness to therapy is more complex than that. There is also the notion of a diffuse, highly personal sense of “readiness” for any medical undertaking (Bartlett, 2002) that has become well-recognized in HIV/AIDS care. Putting this individual and personal sense of readiness together with actual social impediments to therapy, gives a more complete definition to “patient readiness.”
Lucas, Chaisson, and Moore (1999) report that availability of social support systems, patients’ ability to fit medication dosing into their routines, and the sense that they can dose without stigma (take HIV medications in front of others) contribute to adherence. Furthermore, when patients keep clinic appointments, and when they understand that missing doses or taking doses late leads to viral resistance, adherence predictably improves. The Panel on Antiretroviral Guidelines for Adults and Adolescents (PAGAA) (2006) advises that a “trusting relationship” among patient and health care team is essential (p. 2), and that continual communication between patient and team contribute to readiness to therapy as well as adherence. Active substance abuse (Sherer, 1998), untreated mental illness (Kemppainen et al., 2004; Uldall, Palmer, Whetten, & Mellins, 2004), and current living status may interfere with readiness and need to be considered as part of adherence readiness assessment and education planning (PAGAA, 2006). Next, a suggested standard of care for adherence training is considered.

In a study by Murphy, Lu, Martin, Hoffman, and Marelich (2002) several features of what many clinicians would consider to be a “good” adherence training approach were employed in a pilot among 33 patients on ART. Those features include individualized training sessions to discuss readiness for ART, incorporation of the regimen into the patients’ lifestyles, and also strategies not commonly employed in clinics such as group sessions to explain treatment rationales, how adherence influences the development of drug resistance, and so forth. In this study, “standard care” was less formal and was described as “the regular care provided by the clinic as its normal policy” (Murphy et al. p. 60). The authors go on to state that this consisted of
…the usual inquiries at regular appointments as to difficulty with adherence; those reporting problems received a single 30-minute consultation, had their medication schedule written down for them, and received no further intervention. (Murphy et al., 2002, p. 60)

A study by Safren, et al. (2001) highlights the difficulty in coming to a common definition of “standard of care” in preparing a patient to take a complicated regimen of fairly toxic medication, and in which non-adherence may have significant health consequences over the long term. In their study of the use of two psychobehavioral strategies to enhance adherence, the control group or patients in the “self-monitoring condition” (p. 1155) the authors do not even describe what initial education patients received about dosing, what to do on “sick days,” and other potential conditions noted above in the material from University of California San Francisco and AIDS Education and Training Center. In the “Life Steps [intervention] condition” the group received interventions that included “eleven informational, problem-solving, and cognitive-behavioral steps for improving adherence…” which include “obtaining medications…formulation of a daily medication schedule…” and “cues for pill-taking” (p. 1156). Also included are strategies such as guided imagery (GI). The problem is that many of their intervention strategies are included in current educational interventions undertaken by clinicians, nurses, and pharmacists, depending on who is assigned to the task in any given clinic. In the researcher’s experience it is common for several such points to be covered in varying depths by several such agents in a given patient visit—especially if a new regimen is being prescribed, or there has been a change in one or more agents in the regimen. Since the beginning of combination ART for HIV, clinicians and
others involved in care have been teaching patients about dosing times and other items in the list of the intervention by Safren et al.

That clinicians and other staffers may not always address the items noted in the lists above in the same way, style, depth, or detail was the subject of a study by Golin, Smith, and Reif (2004). They sought information about the adherence training habits of a sample of 589 physicians in North Carolina. With a response rate of 63%, 369 respondents reported spending an average of 13 minutes counseling patients who were starting a new or changed regimen, and covered an average of seven of 16 “counseling behaviors” on a checklist developed by the researchers, adapted from items from the Adherence and Efficacy of Protease Inhibitor Therapy Study (ADEPT) provider adherence behavior scale, *The United States Pharmacopeia* (USP) Medication Counseling Behavior Guidelines, and U.S. government guidelines for Medicare. The authors concluded that physicians treating HIV/AIDS patients need additional training in adherence as well as more time to deliver the messages that support adherence. This researcher’s question would be: Given the immense amount of information available in every form: oral presentations, journal articles, websites, and even colleagues in nursing and pharmacy, is it really a problem of “lack of training”?

**Conclusion**

Adherence education is an important part of how patients acquire facility with their medical regimens. Several authorities propose very similar schemes to assure that patients understand the goals of drug therapy, special features of the regimen (e.g., timing with meals), and how to manage side effects, as well as the consequences of nonadherence. Evidence suggests that adherence education in the clinic is variable. On the one hand, it is necessary to assess patients’ knowledge and capabilities and to adapt education appropriately.
On the other hand variability and missed opportunities are common. Reconciling these two issues for this study is discussed in the chapter on methodology.

**Cognitive-Behavioral Therapy for Symptom Management**

Much of the research into the management of symptoms using CBT involves cancer—either the symptoms of the disease itself, or symptoms that arise from treatment. Such experience forms a basis for the proposed study.

It was during the time of burgeoning research into the so-called “mind-body connection” during the 1970s, that pharmacological and radiological interventions for cancer were also gaining greater success against the disease. Such therapies came with serious side effects, ranging from local and systemic pain, to nausea/vomiting, debilitating fatigue, and even anxiety related to such adverse effects, a condition of their use that still obtains today (Golden, 1975; Sausville & Longo, 2001; Schnell, 2003). This resulted in a number of investigators looking into whether techniques effective in achieving autonomic control could also be effective in helping cancer patients achieve greater comfort during treatment cycles. Indirectly, this might improve adherence or willingness to continue chemotherapy. The next section reviews the literature on the management of symptoms, with emphasis on symptoms in cancer and HIV.

**Nausea and Vomiting**. One of the thornier problems in antineoplastic therapy is that of control of nausea and vomiting (Grunberg, Hansen, Deuson, & Mavros, 2002). Most patients find these symptoms highly aversive, and their control is considered one of the keys to successfully engaging patients in continuing chemotherapy. Promethazine, metoclopramide, corticosteroids, and a host of other antiemetics have been used to relieve nausea (Morrow, Roscoe, Hickok, Andrews, & Matteson, 2002; Schnell, 2003). At the time
of this writing, the 5-hydroxytryptamine-3 receptor (5-HT₃) antagonists are demonstrated to be the most effective pharmacologic means of controlling nausea and vomiting (NCCN, 2005). It is understood that serotonin, released from enterochomaffin cells in the small intestine, activates the chemoreceptor trigger zone (CTZ) during some antineoplastic therapy (Schnell, 2003), but what is not understood is why agents such as cisplatin, cyclophosphamide, and doxorubicin have such a high emetogenic potential in this regard. Nevertheless, such agents can be reliably expected to produce nausea and vomiting in most patients (60-90%) (Schnell).

Two conditions related to nausea in antineoplastic therapy cause patients to continue to suffer from the symptom. The first is that although antiemetic therapy has become more effective (Gralla et al., 1999; Grunberg, et al., 2002), not all patients respond to it with complete or significant reduction in discomfort (Gralla, et al., 1999). Second, if control is lacking, and depending on the sensitivity of any given patient to distress related to nausea, some patients become conditioned to expect the nausea and vomiting, and this may lead to ANV (Burish & Carey, 1986; Zachariae et al., 2007). Cancer patients may grow ill on the way to the clinic, or the day prior to a treatment round, or even in situations that remind them of chemotherapy (such as a dentist’s office) (Morrow et al., 1992; Morrow, Roscoe, Kirshner, Hynes, & Rosenbluth, 1998; Schnell, 2003). Zachariae et al.(2007), using several scales of sensitivity and reactivity (Tellegen Absorption Scale, the Somato-Sensory Amplification Scale, and the Autonomic Perception Questionnaire) found that “openness” to absorbing new situations, and suggestibility tended to increase ANV. A review by Morrow, Roscoe, Hickok, and Matteson (2002) supports the view that while newer antiemetics are more effective, nausea and vomiting—anticipatory and otherwise—remain a clinical problem in
antineoplastic therapy. Both medical and behavioral techniques are required to fully address the biological and behavioral reasons for the symptoms.

**Behavioral Interventions in Nausea and Vomiting in Antineoplastic Therapy**

Several studies have shown that relaxation training that helps patients moderate their anxiety may significantly reduce conditioned responses that lead to ANV. Dempster, Balson, and Whalen (1976) describe a case utilizing hypnotherapy as a means to reduce anticipatory nausea and anxiety in a female undergoing antineoplastic therapy with nitrogen mustard for Hodgkin’s disease. She responded well to the intervention and was able to continue with her therapy. She also expressed more “hopeful feelings” (p. 7) about being able to live with her disease and the treatment.

Burish and Lyles (Burish & Lyles, 1979) found that relaxation training allowed a woman to successfully tolerate chemotherapy for lymphoma. Consequently, they followed this with a small trial of 14 participants (cancer type not stated) (Burish & Lyles, 1981) and demonstrated significant \( p<.05 \) improvements in mood (anxiety, anger, and depression as measured by the Multiple Affect Adjective Checklist) and post-treatment nausea (verbal Likert scale developed by the authors) as well as lower physical arousal (pulse rate; differences in blood pressure were non-significant). Similar studies with similar designs and dependent measures confirmed significant trends toward lessened nausea, improvements in mood, and decreased arousal (Burish, Carey, Krozely, & Greco, 1987; Burish & Jenkins, 1992; Burish, Snyder, & Jenkins, 1991; Burish & Tope, 1992; Carey & Burish, 1988). Morrow et al. (1992) were able to show that techniques such as progressive muscle relaxation, directed at reducing nausea in cancer patients undergoing antineoplastic therapy, were generally safe and effective even when delivered by nurses or oncologists. A
psychologist or therapist did not have to be present to deliver such interventions. The authors note that medical personnel should not engage patients in psychotherapy or other interventions that might require the spectrum of skills that would require special training in psychology.

One negative study by Syrjala, Cummings, and Donaldson (1992) found that hypnosis did not significantly reduce symptoms of nausea (although it did reduce oral pain) in the treatment arm of a trial of 67 bone marrow transplant patients. Distraction as a technique, was tested against relaxation in 60 patients assigned to one of six groups in a 2 x 3 factorial design, based on their pre-intervention level of anxiety, and to either intervention or the control condition (Vasterling, Jenkins, Tope, & Burish, 1993). There was no difference between the interventions; both significantly reduced nausea and physiologic arousal (blood pressure).

Over the last several decades, it has been shown that behavioral management is an important adjunct to medical therapies directed at relieving nausea in antineoplastic therapy (Redd, 1994). Later reviews that attempted to determine the most effective behavioral approaches have shown that techniques that reduce physiological arousal and induce trance or semi-trance states such as hypnosis, and relaxation, and cognitive techniques such as guided imagery exert the greatest effects in symptom reduction (Mundy, DuHamel, & Montgomery, 2003; Redd, Montgomery, & DuHamel, 2001).

**Behavioral Interventions Used to reduce Pain:** Acute pain may be managed through cognitive/behavioral means (Chen, Joseph, & Zeltzer, 2000; Kuttner, 1989; Logan, Baron, & Kohout, 1995; Rusy & Weisman, 2000; Tan & Poser, 1982). Chronic pain presents more challenge, and chronic pain has drawn significantly more attention in terms of CBT.
interventions (Adams, Poole, & Richardson, 2006; Eccleston, 2001; Frischenschlager & Pucher, 2002; Morley, Eccleston, & Williams, 1999; Nielson & Weir, 2001; Turk, 2003).

Perhaps this owes to the fact that analgesics are often effective for short-term pain, and acute pain often has a definable proximate cause (e.g., appendicitis, sprain, side effects from drugs).

By the mid-1980s a small number of studies had tested the effectiveness of CBT in the management of cancer pain. Caudell’s (1996) review mixed studies of pain, ANV, and anxiety, as well as great variety of CBT interventions (e.g., distractions, relaxation, etc.)—as well as non-CBT interventions such as Therapeutic Touch—and concluded that such therapies could easily be included in nursing practice, but spoke with less certainly to whether such therapies are effective. It can be argued that Caudell’s review, while admirable for its humanism, did not apply adequate inclusion criteria to her review.

Morley, et al. (1999) contributed a meta-analysis of chronic pain management in patients other than those with cancer. Twenty-five papers met inclusion criteria, and diagnoses included musculoskeletal and neuropathic pain of various types but excluded headache. They concluded that significant effect sizes occurred for all intervention groups, when controls were applied for variations in measurement reliability. In another meta-analysis (McCracken & Turk, 2002) of pain other than that caused by cancer, patients’ sense of control and willingness to participate in their pain management was significantly correlated with effect sizes.

A panel at the U.S. National Institutes of Health (Anonymous, 1996) determined that psycho-behavioral interventions are a useful adjunct in chronic pain management. The strongest evidence for efficacy was for hypnosis and relaxation techniques alone, and
moderate effects for cognitive behavioral therapy (which may or may not include those specific behavioral techniques, as “cognitive behavioral therapy” encompasses a large subset of behavioral supports).

Devine and Westlake (2003) reported on a meta-analysis of 25 studies of adults with cancer pain and the use of CBT. Methodological quality varied considerably; several trials did not employ random assignment. When the analysis was limited to better quality studies, a statistically significant improvement in pain control remained evident, with the most effectiveness seen in trials employing relaxation techniques. In a review (Semple, Sullivan, Dunwoody, & Kernohan, 2004) of the use of psychological interventions as adjunctive pain management in head and neck cancer, studies tended to support the effectiveness of CBT over other psychological interventions. Tatrow and Montgomery (2006), in a meta-analysis of 20 studies of CBT to reduce distress and pain in breast cancer patients found that CBT effect sizes were .49 reduction of pain regardless of whether or not metastasis had occurred. Effect sizes for reducing distress were more modest, averaging .31.

As in the case of nausea and antineoplastic therapy, the perceptions of pain were reduced with CBT, with particular effectiveness of interventions that employed relaxation or hypnotic-type therapies (and guided imagery may be said to obtain this categorization, since it is typically employed after induction of relaxation by other means). Note that this review does not distinguish between pain caused by antineoplastic therapy and pain caused by cancer itself. The meta-analyses above focused on studies of pain as experienced by the cancer patient regardless of cause, the exceptions being the reviews by Redd et al. (2001) and Mundy et al. (2003).
**Note on the Pain and the Side Effects of ART.** It is a generally-accepted axiom of nursing that pain is whatever the patient says it is, and an assumption follows that pain may not have a definable, relievable pathophysiological cause. It is also axiomatic such an assumption arises from exclusion of treatable causes. In clinical experience HIV/AIDS patients have complained of “pain” related to ART, but not always pain that could be related to known side effects or toxicities that are *ordinarily* accompanied by pain. Conversely, pain—or any symptom—may arise from a problem with a given medication. For example, zidovudine may cause lactic acidosis with accompanying abdominal pain (GlaxoSmithKline, 2005). Johnson, Stallworth, and Neilands (2003) examined the causal attributions of symptoms held by HIV/AIDS patients: disease, medicine, or neither (i.e., a non-HIV, non-ART cause, such as reflux disease, heart disease, etc.) They found that such patients generally assigned certain types of symptoms, e.g., adenitis, to the disease. This agrees with what most patients are told about the symptoms of HIV disease. Side effect symptoms tended to be those that could be temporally related to the start of ART or related to dosing times. Their study found that in either case, side effect or disease symptom, correct attribution is not always certain. Patients may mislabel symptoms as side effects and vice-versa, creating problems for clinical interpretation, especially if information is omitted by the patient because they believe a symptom unrelated to medication. More to the point with respect to the current review, is that there is no solid line between symptoms attributable to disease states or ART side effects.

In general, CBT is effective for chronic pain, and evidence supports the use of CBT in cancer/cancer treatment pain. In particular, effectiveness was seen with the inclusion of hypnotic and relaxation-based interventions in this population.
**Behavioral Interventions in Fatigue.** A search for studies that utilized a cognitive, behavioral or dual therapeutic intervention (CBT) to reduce fatigue in cancer patients, returned three studies. Levesque, Savard, Simard, Gauthier, and Ivers (2004) employed cognitive therapy as an intervention for depression in cancer patients in a single group pretest/posttest design. Depression improved, as well as associated symptoms such as anhedonia and fatigue. Given et al. (2004) conducted a randomized clinical trial using CBT as the experimental intervention. Fifteen symptoms were measured by severity on 11-point rating scales (0-10); the scores were then summed to create a scale from 0-150 global score. The intervention included cognitive approaches (e.g., skills development, self-persuasion, problem solving) and behavioral methods, although these are not specifically reported, as they were tailored to each patient’s needs. Global symptom scores improved at 10 and 20 weeks, but the report did not break down the analysis by individual symptom. A very similar study a year later (Sherwood et al., 2005) also demonstrated improvements in symptom scores at 10 and 20 weeks, and again the symptoms were not individually analyzed. A single randomized trial that addressed CBT and fatigue in female HIV patients (Lechner et al., 2003) utilized a cognitive-behavioral stress management/expressive-supportive therapy intervention to improve quality of life (QOL), operationalized with the Medical Outcomes Study 30-item (MOS-30) scale for HIV. The intervention group demonstrated a statistically significant improvement in total MOS-30 scores by analysis of variance ($p<.05$) and overall health distress and health perceptions ($p<.001$), but fatigue, and single-item scores did not change significantly.

Fatigue is a common symptom in HIV patients, and it stems from several causes, some treatable with medication, hygiene, or regimen changes. Other causes are less certain.
Few studies exist—in oncology or HIV care—that examine the effectiveness of CBT in treating this symptom.

**Anxiety.** Anxiety presents a special case. Not only is anxiety itself uncomfortable for the patient, but it tends to potentiate other symptoms. Sternbach (1975) noted that anxiety aggravates pain and suggested the exploration of biofeedback as one means of reducing the anxiety that is both associated with pain, and worsened by it. In the discussion of Burish and Lyles’ (1979) 30-year-old cancer patient with side effect symptoms, her negative affect decreased with CBT and this was associated with concordant decreases in other symptoms such as pain and nausea. In a trial by Lerman, et al. (1990) coping styles that featured information gathering and “monitoring” were associated with heightened anxiety. The higher levels of anxiety correlated with increases in nausea and other physical side effect symptoms in those participants. Coping styles that employed distraction were associated with less anxiety and also blunted physical side effects. Kalichman (1995, pp. 223-224), argues that shifting HIV patients’ locus of control inward helps them to assert power in their own cognitive domain. Since the cortex—thought—is the final common pathway of symptom experience, it seems logical that any therapy that reinforces the patients’ power over thoughts could be expected to blunt or otherwise alter such symptoms as they are experienced.

Starcevic (2006) reviewed conceptual and treatment issues in anxiety and reports that CBT is effective at treating the disorder, not only in clinical trials but in routine clinical settings. In their review of CBT used to treat “ordinary” psychiatric problems such as depression and anxiety, Hollon, Stewart, and Strunk (2006) found that medications were largely palliative, while CBT interventions seemed to show a trend toward more enduring effects. The effects could not be accounted for by methodological issues alone. However,
they do not conclude whether this trend to improvement is the result of ameliorations of factors that led to illness, or to the mobilization of patients’ own psychological skills.

Two meta-analyses were conducted by Sheard and Maguire (1999), one for depression (20 trials) and one for anxiety (19 trials), in cancer patients treated with psychological interventions. Most of the studies used CBT or some variant of CBT. Psychological interventions had a negligible clinical effect on depression, and a moderate effect on anxiety (mean effect size .36), with the most robust effects seen in four trials that focused on prevention (.94) of anxiety. In summary, CBT is effective in reducing anxiety, although it is not certain how much improvement represents individuals’ adaptations over time, and the role of medications and other medical changes.

**Antiretroviral Therapy and CBT**

**Side Effect Symptoms and Adherence to ART.** Several studies looked at the impact of side effects on patients taking ART. Ammassari et al. (2001) undertook a multicenter, descriptive study that examined correlates of adherence. Patient’s level of side effects on a 16-item symptom questionnaire significantly inversely correlated with level of adherence, with greater number and intensity of side effects associated with lower levels of adherence. Brook et al. (2001) examined reasons patients chose to skip doses and/or discontinue otherwise successful regimens in a twelve-center study in England. Lack of motivation was found to have the largest impact leading to poor adherence, but side effects were a statistically significant factor in their descriptive study.

Regimen selection has been proposed as a means of improving adherence, based in part on a study by Miller, Huffman, Weidmer, and Hays (2002), which found that anticipated side effects have an impact on patient preferences for various regimens. The authors argue
that factoring anticipated side effects and patients’ individual tolerance for various such
effects could improve adherence, and improve clinical endpoints. A grounded theory study
by Wilson, Hutchinson, and Holzemer (2002) proposed a theory of nonadherence that
encompassed self-identity, illness ideology, concurrent treatment regimens, the meaning of
time, medication burden and side effects, and lifestyle, that coalesce to produce a state of
mind that shapes adherence choices on a dose-by-dose basis. Some of their suggestions for
intervention include education about side effect management, with reframing among them.
No studies have specifically tested this theory. Based on the foregoing work, subsequent
studies have explored the educational and the cognitive/behavioral approach, respectively. In
a prospective pilot study, medication adherence improved with the use of weekly medication
counseling sessions, focused on various management issues, and including a pill organizer
(McPherson-Baker et al., 2000). Similar results were found in a prospective study of 997
patients (Weiss et al., 2003). Knowledge about ART was significantly associated with
adherence. Using logistic regression analysis to analyze the number of correct questions out
of five, fewer than four correct answers increased the odds of self-reported nonadherence
(OR = 1.72 for 2-3 correct, p<.01; OR = 2.92 for 0-1 correct, p<.05). Gellaitry et al. (2005)
studied patient satisfaction with medication education in 115 participants. Using a validated
questionnaire, the authors found that patients who reported less satisfaction with the
information they received about ART to be more likely to decline therapy (p<.05). Declining
ART was significantly associated with concern about potential adverse effects of therapy
(p<.001). The authors conclude that individualizing education may improve acceptance of
ART. The most significant feature of these studies is that the dependent variables were all
based on patient adherence, with clinical endpoints (CD4 and HIV RNA) not measured—
these were assumed to improve because of adherence, as noted in earlier sections of this paper.

A review by Haddad et al. (2005) of the available trials of educational interventions to improve adherence, found that only one trial included the a comparison group and a measure of adherence. Their conclusion was that only a pharmacist-led educational intervention improved adherence significantly. Improved adherence in that study was associated with viral loads below the limit of detection, regardless of participation in the intervention. In other words, participating in the intervention did not statistically predict undetectable viral load, only improved adherence, regardless of how patients got there. The authors also noted that more trials looking at clinical endpoints should be considered for study.

The Use of CBT in ART. The review sought to answer two questions. The first question asked to what extent have CBT approaches been used to either mitigate symptom side effects in ART, or to improve adherence (whether or not symptom control was tested)? The second question asked if such techniques have been used, which techniques were most effective in HIV/AIDS and ART?

During the period February 2004 to December 2006 a series of searches were conducted in Pubmed/MEDLINE, CINAHL, and PsyLIT databases. Search terms that would encompass cognitive-behavioral therapy (e.g., “cognitive therapy,” “behavioral therapy,” “relaxation”) were joined with terms to encompass ART/therapeutics, medication adherence/compliance, and HIV and/or AIDS. In the most recent search, 18 studies were cataloged. Six of these studies met the criteria for inclusion: An individualized cognitive, behavioral, or combination approach was the intervention in a clinical trial, pilot study with or without control, or case series. The intervention could affect any variable related to
adherence or symptom control (including mood, or cognitive processes that could help improve mood). The six studies are summarized below.

Using a pre-test/post-test design among Taiwanese HIV patients, Chiou et al. (2004) found that fewer hospital visits occurred among HIV patients on ART when an educational intervention was used to teach management of side effects. This three-arm trial compared a control group, and two experimental groups, one which received a group therapy intervention, and the other which received individualized therapy. The control received “standard” teaching on medication use. Hospital visits decreased in both group and individualized interventions, but there was no statistical difference between the two groups. Although the clinical endpoints for HIV and adherence were not studied, the authors conclude that a reduction in hospital visits reduces burden on the health care system and gives HIV patients on ART the tools to manage side effects effectively. The study was included here based on the assumption that symptom control could serve as a reason a patient would visit the hospital (“visit” included visits to emergency wards, even if the patient was discharged the same day).

The remaining four studies examined the impact of CBT. Two small studies (Ironson et al., 2001; Murphy, et al., 2002) examined the use of CBT to increase self-efficacy among HIV patients, as it affects adherence, clinical endpoints, and perceived distress. Murphy, et al. (2002) sought to test the hypothesis that enhanced self-efficacy—the ability to assert oneself with clinicians, ask questions, report problems, etc.—would lead to improvements in adherence, less distress, and greater life satisfaction. Twelve participants were randomized to receive standard medication education (SME) or SME and cognitive/behavioral interventions designed to enhance self-efficacy (e.g., coping strategies, engaging social support).
Reframing, relaxation, and distraction, were not among the CBT techniques used, and there were no CBT interventions devoted solely to management of side effects or distress related to side effects. A statistically significant improvement in self-efficacy was found using the Antiretroviral Medication Adherence Coping Strategies Scale, which was used to measure patient-physician communication, social support, and acceptance of need for medication \((p<.05)\). However, there was no significant difference between groups for adherence, measured by self-report (although the authors report a trend toward significance). This may result from the small number of participants \((n = 33)\).

Ironson et al. (2005) looked at whether CBT might have an impact on self-efficacy and disease markers (CD4 and viral load). In a randomized, controlled clinical trial with 56 women, the researchers tested the question: does self-efficacy improve clinical endpoints in HIV disease? Fifty-six women were randomized into intervention and control groups. The intervention targeted general measures of self-efficacy, operationalized in a self-efficacy measurement tool developed by the authors. The actual intervention emphasized reframing thoughts about ART, developing assertive responses (e.g., asking questions when some technical aspect of ART wasn’t understood clearly), and relaxation techniques. Clinical endpoints improved in the intervention group; the results were statistically significant. Adherence was not measured. However, the authors discuss that it is unclear as to how or why CD4 counts improved and viral load decreased: was it greater adherence or some as-yet-under described effect of thought on the subjects’ immune systems?

Two studies (Jones et al., 2003; Parsons, Rosof, Punzalan, & Di Maria, 2005) examined the how the choice of CBT strategy might change adherence. Jones et al., in a study of 174 low-adhering women randomly assigned 82 women to a ten-session psycho-
educational intervention, based on principles of cognitive therapy and stress management, that was designed to encourage the women to express their concerns, beliefs, and knowledge of ART, including its potential impact on their lives and the courses of their disease. The intervention was intended to improve coping, and was not designed to improve adherence, although it was hypothesized that adherence might improve. Denial-based coping did improve in the intervention group, and low-adhering women did increase their self-reported adherence by 30% ($p<.01$). Adherence in the control group did not improve.

The study by Parsons et. al. (2005) focused on substance abuse as a main factor contributing to non-adherence. They sought to test a cognitive-behavioral intervention that would prevent relapse as well as preventing behaviors in which substance abuse would interfere with regular ART dosing. As in the study by Jones, et al. (2003) the intervention was based heavily on engaging cognitive processes, through the use of classical cognitive therapy and motivational interviewing. Eleven participants completed the full eight weeks of sessions with the therapists, and the remaining four completed between two and six sessions, with twelve participants available for the final three-month follow up evaluation. The authors report that the study was too small to show an effect. However, a non-significant trend toward improved adherence was evident.

Two studies (Molassiotis et al., 2002; Molassiotis, Lopez-Nahas, Chung, & Lam, 2003) sought to examine the impact of CBT on adherence. In a pilot study (Molassiotis, et al., 2002) of 46 Chinese patients that used a group CBT intervention there was a statistically significant improvement in both mood (Profile of Mood States) and quality of life (World Health Organization Quality of Life-BREF-HK Scale). Because it was a group intervention, it does not strictly meet the criteria for this review. It is included here because it formed the
basis for a second study by Molassiotis, Lopez-Nahas, Chung, & Lam (2003), 12 Chinese patients using individualized CBT, with most of the emphasis on cognitive strategies, especially education about medication use. This study also found statistically significant improvements in adherence (self report) and CD4 counts in the intervention group (t-test of means from AIDS Clinical Trial Group [ACTG] Adherence questionnaire, p<.05). The authors conclude this is due to greater adherence to medications. The five studies that focused on individualized interventions are summarized in Table 2.1.

Discussion: The use of CBT in improving symptom control during ART has not been studied. The existing literature suggests that CBT has been used to effectively improve adherence to ART. Most of the interventions emphasized the use of cognitive strategies: reframing maladaptive thinking about ART, improving coping skills, and confronting concerns and beliefs about ART. Two studies (Ironson, et al., 2001; Molassiotis, et al., 2003) demonstrated a statistically significant improvement in clinical endpoints (CD4 count and viral load). The studies tended to be limited by small sample sizes (Jones, et al., 2003; Molassiotis, et al., 2003; Parsons, et al., 2005), and the number of sessions, which numbered from eight to 12 (Jones, et al., 2003; Molassiotis, et al., 2002; Molassiotis, et al., 2003; Parsons, et al., 2005). In each of the latter three studies, attrition contributed to decreasing sample size over the courses of each study (all of which ranged from three to six months). Further this suggests that interventions that require many sessions with the therapist might tend to lose patients—and thus, efficacy—over time.

The studies discussed suggest that CBT may help improve adherence to ART, but none of the studies tested whether symptom control could be effectively achieved using CBT.
Table 2.1 Studies of CBT in ART.

<table>
<thead>
<tr>
<th>Study</th>
<th>CBT Intervention</th>
<th>n</th>
<th>Design</th>
<th>Variables</th>
<th>Results</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy, et al (2002)</td>
<td>Cognitive therapy to improve self-efficacy</td>
<td>33</td>
<td>RCT</td>
<td>Adherence by self report</td>
<td>Higher self-efficacy in intervention group; NS changes in adherence</td>
<td>Authors suggest a larger trial.</td>
</tr>
<tr>
<td>Molassiotis et al (2003)</td>
<td>Education &amp; counseling to maintain adherence to ART</td>
<td>12</td>
<td>One group repeated measures</td>
<td>Adherence by self report</td>
<td>Intervention increased adherence from baseline</td>
<td>Individualized education and counseling improves adherence to ART.</td>
</tr>
<tr>
<td>Ironson, et al (2005)</td>
<td>Self-efficacy &amp; HIV disease markers</td>
<td>56</td>
<td>RCT</td>
<td>Self-efficacy</td>
<td>Self-efficacy correlated with improvement in CD4 and viral load; reduced distress in CBT group.</td>
<td>CBT not targeted directly at side effects.</td>
</tr>
<tr>
<td>Parsons, et al (2005)</td>
<td>CBT to reduce substance abuse and increase adherence</td>
<td>12</td>
<td>One group</td>
<td>Adherence by self report</td>
<td>Decrease in substance use No changes in adherence</td>
<td>Short, small n</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial. CBT: cognitive behavioral therapy. ART: antiretroviral therapy. NS: non-significant.
Furthermore, there was little use of behavioral techniques such as muscle relaxation. The reports suggest that most of the interventions focused on cognitive techniques such as education about ART.

**Gaps in the Literature**

Cognitive-behavioral therapies have been tested in patients with cancer, HIV, and other diseases, both psychological and physical. The focus of this review has been on the use of CBT to reduce symptom intensity and frequency in patients taking ART. In the first section, six studies tend to suggest that adherence improves when a type of CBT is the intervention, but the specific elements of CBT in each study varied. Thus, it is somewhat difficult to draw conclusions about the most effective combination of techniques, which include cognitive (educational, skill-building, coping, guided imagery, self-persuasion) and behavioral (relaxation, distraction, behavior modification). However, when the literature on CBT interventions in cancer care is included, some combination of education/reframing, guided imagery, hypnosis, and relaxation emerge as preferred choices for designing an intervention. In the studies of HIV and CBT, adherence generally improved, but no study used side effect symptoms and adherence as a set of dependent variables.

**Summary**

Infection caused by HIV is life-threatening and persistent. Viral suppression is the main goal of treatment, and leads to increases in CD4 counts and a reduction in opportunistic infections and HIV-related mortality. Moreover, the HIV genome is highly mutable, leading to the daily occurrence of drug-resistance mutations, which become more hazardous when medications are taken inconsistently. Thus, ART must be continued definitely. Yet adherence remains a problem. Forgetfulness, substance abuse and other behaviors may interfere with
adherence. Side effects from medication—experienced, or simply feared—also interfere with successful ART, whether because patients discontinue medications, or because their fears prevent them from undertaking ART in the first place.

Adherence education has become a standard of care in the management of HIV patients who consider taking, or who continue on, ART. Thorough, detailed instruction in the use of medications, dosing, how to manage side effects, and other aspects of medication taking has been shown to improve adherence. Psycho-educational interventions (e.g., counseling, individualized education) have also improved adherence in some studies, but not in all studies. Whether psycho-educational interventions will improve adherence remains an open question, and may depend on techniques that are used.

Side effects may interfere with medication taking, and this is also true in cancer chemotherapy. A significant body of research supports the use of CBT in the management of pain, anxiety, and nausea/ANV for such patients. The literature is silent on whether this affects adherence to ANT, but such interventions definitely improve patient comfort and sense of control. The literature contains four studies that looked specifically at whether CBT or related psycho-educational interventions could improve adherence. Results suggest that individualized CBT may improve adherence. Two studies were of such interventions, but with self-efficacy/self-esteem (SE/SE) and hospital visits as the dependent variables, and in general, improved SE/SE reduced hospital visits (assumed to correlate with disease severity) and improved CD4 counts. No study looked specifically at whether CBT could be used, as it has been in oncology, to reduce side effect symptom severity, and whether this would then affect adherence in a positive way.
Chapter 3

Methods

Research Design

This was a two group, randomized, controlled clinical trial. Both groups (experimental, control) received the standard of care (SOC) (adherence education) from their clinicians at their regularly-scheduled office visits. The experimental group also received the intervention at three time points \((I_1, I_2, I_3)\). Three categories of measurement (symptom scores by VAS, SF-36, and clinical laboratory data) were to be obtained at four time points. It was planned that each participant in the control group would be measured at study entry and three more time points, each about a month apart, until measurements were obtained for a three-month period. Participants in the experimental groups would be measured at similar intervals, with some allowances for scheduling with the behavioral interventionist, and each measurement to be performed just prior to each of those three visits. The major advantage of experimental design is its power to resolve research questions by active, prospective comparison to controls, and thus to establish support for causality between the intervention and the outcome. Limiting and/or controlling for confounders is another advantage of the prospective design, and randomization contributes to that effort through the assignment of attributes across both groups (Polit & Beck, 2004).

Setting

The study was performed in an academic medical center infectious disease clinic in South-central Pennsylvania. The cognitive behavioral therapy (CBT) interventions were delivered in a quiet conference room with low lighting and comfortable chairs. The setting offered access to approximately 1200 HIV patients, 90% of whom were on ART at any given
time (J. Zurlo, personal communication, March 19, 2007). The center is part of the AIDS Clinical Trials Group (ACTG) and is a federally funded HIV treatment center. The clinic itself is also an outpatient cancer treatment center, with designated days during which HIV/AIDS patients are scheduled.

Sample

Pre-trial discussion with the clinic’s physicians suggested that enrollment could be significantly limited if random sampling was utilized; therefore, convenience sampling was planned. The medical center’s institutional review (detailed further later) specified that participants would be pre-screened by a clinic physician or nurse, and if the patient agreed, the primary investigator (PI) could then explain the study in detail and offer the opportunity to consent. It was planned that participants would be randomized to the experimental or control group until the enrollment was filled. Rolling enrollment was to continue until 30 participants completed the study. Power analysis is described in a later section.

University- and institution-approved posters advertised the study. The PI attended clinic each day that the nurse case manager (NCM) reported that there would be potential participants available. (The clinic also mixed in many general infectious disease patients, so some days no or few HIV patients were scheduled.) On occasion, clinic physicians also notified the PI that a patient would be a suitable candidate for participation.

Eligibility Measures

The PI planned to recruit men and women, 18 years of age or older, who could read and understand English, and who could give an informed consent. Participants on ART were eligible if they affirmed that they suffered from one or more symptoms of nausea/vomiting,
fatigue, pain, and/or anxiety related to side effects. Participants had to have been on ART prior to study entry, but no minimum duration on ART was required.

A demographic questionnaire (Appendix A) was used to collect data to describe the population and to determine eligibility requirements, and to confirm that participants were actively symptomatic. Data were collected on age, race, education, and other attributes and these were used to describe the population under study. Data on which of the four specific symptoms participants suffered from were also collected.

**Subjective Health Measures**

**Specific symptom measures.** Visual analogue scaling (VAS) was selected to quantify the four symptom variables (nausea, pain, fatigue, and anxiety). The four symptom variables selected are based on the author’s clinical experience when faced with patients who had or stated they would discontinue ART due to side effects.

Table 3.1

Symptom Variables

- **Nausea:** to be understood as nausea, “upset stomach,” or other unpleasant upper-gastrointestinal sensations that the participant associates with medication use.
- **Pain:** as felt by the participant; any pain is included.
- **Fatigue:** to be understood as “tiredness,” “being wiped out,” or other terms, as felt by the participant.
- **Anxiety:** or “a sense of worry,” “dread,” or “feeling nervous” insofar as it relates to treatment or the disease itself (as it may be hard for participants to distinguish the two).

Visual analogue scaling was developed to measure patients’ experience of pain (Keele, 1948). Subsequent refinements included the option of horizontal orientation and the use of straight lines without numerical marks, and with the use of verbal descriptors at either
end of the scale, reflecting the absence of a symptom to the perceived worst imaginable experience of that symptom (Gift, 1989). Cline, Herman, Shaw, and Morton (1992) proposed standardization of the VAS at 100mm, although other lengths have been proposed for other purposes, such as measurement of “absolute” pain and “comparative” pain (Carlsson, 1983). Wewers and Lowe (1990) reviewed how VAS has also been applied to the measurement of nausea, vomiting, anxiety, mood, dyspnea, a host of other subjective complaints.

**Reliability and validity of VAS.** Visual analogue scales are reliable and valid. Brunier and Graydon (1996) tested the reliability and validity of VAS against a Likert scale in the measurement of fatigue. McCann and Boore (2000) used the 4-item vitality scale in the SF-36 as a measurement of the opposite state of fatigue, and as a validity check on scoring of the other measures in their study of fatigue in renal dialysis patients. In a study of general fatigue and breathlessness in healthy volunteers (Grant et al., 1999), the VAS demonstrated reproducibility coefficients of 78%, with correlations to physical demand measures ranging from .73-.82. Lingjaerde and Føreland (1998) tested 162 patients with seasonal affective disorder, and compared their VAS scales for global improvement after light-box therapy to the Montogomery-Asberg Depression Rating Scale (MADRS) and a scale for atypical depression symptoms (ATYP). Changes in VAS correlated closely with changes in MADRS \((r=.85)\) and moderately well with ATYP \((r=.64)\). Test/retest reliability was .96 for two consecutive ratings during a period in which participants reported no change. Muth, Stern, Thayer, and Koch (1996) designed a nausea assessment profile and tested it against VAS in a four-stage study involving over 1500 student volunteers. The purpose was to exhaustively describe nausea as a sensation, test the scale in a group affected by motion sickness versus control, and then to test correlation with VAS completed by participants. Correlation of .71
with VAS was found. In pain measurement, De Conno et al. (1994) tested 53 patients with cancer pain with 5 different rating scales, and a sixth at follow up after treatment of pain (to evaluate change). The VAS and the numerical rating scale showed the strongest association with absolute values of pain. Mottola (1993) suggests that VAS allows patients to render continuous, subjective, abstract sensations into data without having to describe these sensations in concrete terms. In this study, the VAS was used to measure nausea, fatigue, pain, and anxiety. Participants were asked to rate these symptoms a total of four times. At each time point a total of three scales were provided to allow the participants to rate three dimensions of each variable. The VAS instrument used in the study is shown in Appendix B. The anchors selected for the 4-week recall VAS were selected for their generality and their extremity, as patients can be relied upon to render their general sense of how badly they have felt or for how long in such terms (Gift, 1989). The 4-week recall was selected to coincide with both the SF-36 and the interim between measurements.

In conclusion, high correlations with other types of scales and greater variability of scores have been seen in other studies of the VAS (Guyatt, Townsend, Berman, & Keller, 1987; Price, Bush, Long, & Harkins, 1994; Winstead-Fry, 1998), furthermore, the VAS seems to work well across various educable populations and for different symptoms (other than pain, which has been best studied) (Borjeson et al., 1997; Folstein & Luria, 1973; Guyatt, et al., 1987; Lee, Hicks, & Nino-Murcia, 1991; Winstead-Fry, 1998).

The VAS has been used in measuring symptoms in studies of persons with HIV. Youle and Osio (Youle & Osio, 2007) utilized the VAS to measure pain in patients receiving acetyl L-carnitine as a treatment for neuropathy. Reductions of pain in the intervention group tended to be reflected in reductions in pain scores in both the McGill Pain Questionnaire and
the Total Symptom Score instruments, although the authors did not report specific correlation coefficients. Beal et al. (1995), in a study of the efficacy of dronabinol (Marinol®, Abbott Park IL) for anorexia associated with weight loss in persons with HIV used the VAS to measure appetite, mood, nausea, and vomiting. Fatigue was measured in HIV patients using VAS in a comparison study of methylphenidate and pemoline lessening that symptom (Breitbart, Rosenfeld, Kaim, & Funesti-Esch, 2001). The authors (Grant, et al., 1999) report that the Piper Fatigue Scale (PFS) was used as the primary measure of the dependent variable because it is well-validated. Changes in the Energy Subscale of the VAS for fatigue (VAS-F) showed significant improvement along with the changes in the PFS. The VAS-F is 18 items related to fatigue and energy, scored using VAS-type scales for each item (Lee, et al., 1991).

**Sensitivity.** The VAS is sensitive to changes in symptom experience. Ohnhaus and Adler (1975), in a study of six subjects, compared the verbal rating scale (VRS) for pain to the VAS. They concluded that the VAS had greater sensitivity to changes in pain after the administration of pentazocine and attributed this sensitivity to the “continuous” nature of the VAS, allowing for finer discriminations to be made by subjects in reporting changes. A similar study with similar findings using nausea as the dependent variable was undertaken by Borjeson et al. (1997). Again, VAS demonstrated great sensitivity to change, with a change in one step on a verbal category scale being associated with an average change of 20 mm on 0-100 mm scales for nausea intensity, with good agreement between verbal and VAS scales.

There are other instruments that are specifically designed to measure symptom scores in persons with HIV. The HIV Assessment Tool was developed by Nokes, Wheeler, and Kendrew (Nokes, Wheeler, & Kendrew, 1994) and tested in 60 persons with HIV infection, 43 with AIDS (defined by the Centers for Disease Control 1987 criteria), and 53 healthy
controls. The tool performs well, with test-retest reliability of .96, Cronbach’s alpha of .92, and good correlation with Karnofsky performance status ($r = .51$). Face, content, and construct validity were also established. The 34-item scale uses VAS-type scaling, but does not include questions specifically related to nausea, a symptom the author of the proposal specifically seeks to measure. It also inquires about many symptoms that, if medication related, suggest that a serious adverse event requires investigation and possible regimen change (e.g., skin rash, skin sores, cough, bleeding, etc.).

The Sign and Symptom Checklist for persons with HIV disease (SSC-HIV) (Holzemer et al., 1999) was expanded the number of symptoms and includes nausea as a symptom. It also includes a variety of pain items by region (e.g., headaches, chest pain) as well as a specific reference to “fatigue” (as opposed to “tiredness” in the HAT instrument). The collected symptoms better describe the general discomforts often reported from ART (e.g., gas, bloating) but still include many symptoms not under study here (e.g., wheezing, chills). Moreover, the questionnaire is scaled “mild-moderate-severe” and thus loses the continuous scalability of scoring available with VAS.

**General health measures.** The SF-36 was developed to measure a range of health outcomes by Ware and Shelbourne (1992), for the Medical Outcomes Study (MOS), a multi-year research project designed to study patients with chronic conditions (Tarlov et al., 1989). The SF-36 is a self-administered instrument designed to measure interlocking domains. The SF-36 measures limitations of physical activities, pain, general mental health, limitations of usual role activities, vitality, and perceptions of general health (Ware & Sherbourne, 1992).

It should be noted that shorter forms related to multidimensional outcomes measurement do exist (e.g., Short Form-18, Short Form-20 [SF-20], SF-30-HIV), and indeed
such instruments are arguably more efficient to administer and would perhaps be easier to complete by study participants. However, Ware and Shelbourne (1992) present data that supports their assertion that some precision is lost in the use of the shorter scales, and that the somewhat longer SF-36 captures more real world types of limitations in function. For example, the SF-20 only offers one social functioning item. The developers found that adding a second item increased content validity for this sub-domain of overall function (Ware & Sherbourne, 1992). The developers also felt that the SF-20 did not adequately capture dimensions of health and function as these pertain to energy, lack of tiredness and similar concepts, and so added a *vitality* subscale. This addition was based on data from the National Health and Nutrition Examination Surveys (Stewart & Ware, 1991).

The SF-36 is well-validated, reliable, and is normalized to the general United States population (Hays, Sherbourne, & Mazel, 1995; McHorney, Ware, Lu, & Sherbourne, 1994; McHorney, Ware, & Raczek, 1993; Stewart & Ware, 1991; Ware, 1987). The use of the SF-36 in the proposed study of HIV patients on ART would provide another set of measurements to compare to those VAS scores for specific symptoms (pain, fatigue, etc.) and provide numerical data on other quality of life dimensions, such as vitality, function, role, and emotion. There is one item on the SF-36 that asks if the respondent feels his/her health is better, worse, or unchanged from one year ago. This reflects the customary use of such instruments in longer-term studies such as the MOS. However, subsequent developments in the SF-36 have led to the production and testing of versions that allow for shorter terms of recall, and thus shorter intervals of change (Ware, 2005). The SF-36 was administered at each of the four time points described, and takes approximately 10 minutes to complete.
<table>
<thead>
<tr>
<th>Concepts</th>
<th># of Items</th>
<th># of Levels</th>
<th>Meaning of Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reported Health Transition (HT)</strong></td>
<td>1</td>
<td>5</td>
<td>Believes health is much better than a year ago. Performs such activities— even the most vigorous— without limits due to health.</td>
</tr>
<tr>
<td><strong>Physical Functioning (PF)</strong></td>
<td>10</td>
<td>21</td>
<td>Limited in performing physical maintenance. Conceptually related to “ADLs” (activities of daily living). Performs such activities— even the most vigorous— without limits due to health.</td>
</tr>
<tr>
<td><strong>Role—Physical (RP)</strong></td>
<td>4</td>
<td>5</td>
<td>Problems with work or other activities. Conceptually related to “IADLs” (instrumental ADLs). No problems with work etc. related to physical health.</td>
</tr>
<tr>
<td><strong>Bodily Pain (BP)</strong></td>
<td>2</td>
<td>11</td>
<td>Severe, limiting pain</td>
</tr>
<tr>
<td><strong>General Health (GH)</strong></td>
<td>5</td>
<td>21</td>
<td>Evaluates health as poor and believes it will get worse. Feels full of pep and energy all of the time. Feels peaceful, happy, and calm all of the time.</td>
</tr>
<tr>
<td><strong>Vitality (VT)</strong></td>
<td>4</td>
<td>21</td>
<td>Feels tired and worn out all the time. Physical and/or emotional problems severely interfere with social activities. Normal social activities without interference.</td>
</tr>
<tr>
<td><strong>Social Functioning (SF)</strong></td>
<td>2</td>
<td>9</td>
<td>Problems with work or other daily activities resulting from emotional problems. Feels of nervousness and depression all of the time. No problems with work or other daily activities resulting from emotional problems.</td>
</tr>
<tr>
<td><strong>Role—Emotional (RE)</strong></td>
<td>3</td>
<td>4</td>
<td>Problems with work or other daily activities resulting from emotional problems.</td>
</tr>
<tr>
<td><strong>Mental Health (MH)</strong></td>
<td>5</td>
<td>26</td>
<td>Feels of nervousness and depression all of the time.</td>
</tr>
</tbody>
</table>

Note. “Items” refers to the actual instrument questions, of which there are 36 and “levels” refers to the number of items that contribute to that domain score. There are eight domains, as described above, and one “health transition” score.

**Adherence Measures**

This study also used a VAS for participant estimates of average adherence over the past month (Walsh, Mandalia, & Gazzard, 2002), as well as 3-day recall (Chesney et al.,...
2000; Giordano, Guzman, Clark, Charlebois, & Bangsberg, 2004). The instrument designed by Chesney, et al. was structured, complex, and also inquired about specific reason for missing medication doses, and other data. Oyugi et al. (2004) employed the 3-day recall in its more common form: doses prescribed and doses taken over the last three days. That is how the instrument was used in this study.

There are several measures of adherence that have been explored for use in research studies including biological assays of drug levels or for drug metabolites, pill counts, self-monitoring/self-report, clinician estimates (Dunbar, 1980; Murri et al., 2004), electronic monitors (Diaz et al., 2001; R Gross, Bilker, Friedman, & Strom, 2001; Hinkin et al., 2002), and interviews, which may or may not include the use of scales (such as VAS, numerical rating scales, etc.) (Holzemer, et al., 1999; McPherson-Baker, et al., 2000).

Electronic monitoring is expensive (AARDEX Group, 2007; Lamb, n.d.) and correlations with patient self-report is fairly good, (Melbourne et al., 1999) although patients tended to report a few percent higher adherence in the study by Melbourne et al.

Unannounced pill counts (UPC) can be used, and are a less expensive measure of adherence. In a study that compared 3-day recall UPC and a VAS for adherence Giordano, Guzman, Clark, Charlebois, and Bangsberg (2004) found that the correlation between VAS and UPC was high ($r=76$) and the difference between VAS and 3-day recall was non-significant. Moreover, there was a trend toward inverse correlation between data from VAS and viral load measurements ($r=-.49$, $p<.30$), suggesting that participants who were taking their medications regularly and on time also tended to have better suppressed virus. Walsh, Mandalia, and Gazzard (2002) VAS adherence data correlated strongly with MEMS Caps data ($r=.63$, $p<.001$), pill counts ($r=.75$, $p<.001$), and an author-designed adherence
inventory. Again, VAS was inversely correlated with viral load. This study uses a single VAS to measure medication recall “since your last visit,” as it can be argued that this reflects real-world adherence monitoring. Adherence was measured four times at T₁, T₂, T₃, and T₄.

Adherence scores by VAS were rated on a 100mm scale. A score of 100 equates with reported perfect adherence. In this study the data from the 3-day recall was converted to an index:

\[
\frac{\text{Doses taken}}{\text{Doses scheduled}} = x
\]

Thus \(x\) becomes a number between 0 and 1, and represents a percentage. For example a result of 0.5 meant half the doses were taken.

**Control Measures**

The use of side effect reducing medication (SERM) was measured, as it was considered a potential confounding variable. It was not hypothesized that participants in the intervention group will use less such medication than controls. Measuring the use of such medication would allow for statistical control of this variable in the analysis. A flow-sheet style diary (see Appendix C) was included in the measurement tools given to each participant. The diaries were designed to cover the approximately one-month span between each of the four measurements. Thus, each participant had to turn in three diaries. Participants were asked to record their use of various SERM, for nausea, pain, and anxiety. Participants were instructed that over-the-counter and prescription drugs were to be included, and they were told they did not need to specify which drugs they used. Drugs for fatigue were not included in the diary, because there are no drugs approved for the treatment of fatigue as
a symptom, by the U.S. Food and Drug Administration. The measure was intended to capture only the number of doses being consumed for the other three symptoms.

**Immunologic Measures**

**Viral load.** This study used viral load data from chart reviews. Recommendations for the management of stable HIV patients call for testing serum virus levels and CD4 lymphocyte counts every three months (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2009). These data were to be collected at two time points including baseline, \( T_1 \), no more than one month prior to or after starting the study, and at the end \( T_4 \), within two weeks before or up to one month after a given participant’s completion. Although there was one research site, due to insurance requirements for individual participants, some participants had to obtain their tests from other laboratories. Because of this measurement variance from laboratory to laboratory variance was a concern. With advances in both technology and regulation this concern was believed to be less of a confounder than in the past. The planned timing of laboratory studies was discussed with the study site lead physician.

Patients’ viral loads were expected to be reported from either branched-chain DNA (bDNA) assay or by polymerase chain reaction (PCR) assay. Branched chain DNA assay, a variant of PCR, might be more sensitive to low levels of virus, less dependent on taxonomy, and exhibit less error than PCR of the reverse-transcriptase gene (RT-PCR) (Grimes et al., 2003). Today, bDNA and RT-PCR achieve detection of virus down to less than 10 copies/mL, although commercial assays with detection limits from <200 copies/mL to <25 copies/mL are more common, with the preponderance of laboratories providing detection limits on the lower end of that range. Detection limits are further discussed in Chapter 4.
Interlaboratory variation regionally. Regional variance in viral load testing was studied (Kellogg, Atria, Sanders, & Eyster, 2001). In that central Pennsylvania population, the authors were able to conclude that changes in measured virus levels less than $0.50_{\log 10}$ were likely due to testing variation. Changes equal to or greater than $1.00_{\log 10}$ are considered to be clinically significant. Inter-laboratory variance was considered as a potential problem, and the findings related to such variation are discussed further in Chapter 4.

Regulatory controls on variation. The Clinical Laboratories Improvement Act (CLIA) of 1988 provided a legal basis for the enforcement of compliance and competency standards in clinical laboratory testing. Although the U.S. Center for Medicare and Medicaid Services (CMS) has monitoring and enforcement jurisdiction over laboratory testing, third-party accreditation agencies normally conduct routine evaluation of competency and compliance (CMS, 2006). (The College of American Pathologists [CAP] and Joint Commission for Accreditation of Healthcare Organizations [JCAHO] are two of the major accreditation agencies in this regard [N. Sheaffer, personal communication, December 7, 2006.]) All of the laboratories that participants might use would be subject to CLIA, and this fact provided a modicum of certainty that interlaboratory variation would be minimized.

CD4+ lymphocyte (CD4) count. This study used CD4 counts from chart reviews at $T_1$ and $T_4$, and—since these are usually drawn together—the same timing criteria discussed in the section on viral load. Concerns about variation among laboratories applied here as well. “Single platform” flow cytometry (FC) analysis has recently become a more common means of measuring CD4 counts. Such systems have used cell-sized, fluorescent-tagged beads of fixed amounts as controls added to the FC sample, enabling an actual counting of all signals (C. Boyer, personal communication, December 7, 2006; Beckton, Dickinson, &
Single-platform testing has been shown to be a more accurate measure of absolute THC in whole blood (O'Gorman & Nicholson, 2000). The laboratories used in this study are CLIA-certified (C. Boyer). Against the standard calibration standards no more than 2% variance is likely. Laboratories in each geographic location each tested a sample with a CD4 count of 100, the widest potential variance between their results would be 98-102 cells/mm$^3$ (N. Sheaffer, personal communication, December 7, 2006).

**Standard of Care and Experimental Intervention**

**The standard of care (SOC): adherence education.** The importance of adherence and recommendations for adherence training were established in Chapter 2. The SOC for this study is “usual care,” which is described in this section.

During the practical coursework prior to the proposed study, from February to April 2006, this PI conducted observations of clinical encounters at the treatment sites that were approached for the present study. All clinics were Ryan White-funded entities. Two of the fours clinics were hospital affiliated, one was a satellite site of a major academic medical center, and one a private, non-profit clinic.

During the observation period, the author recorded notes on 10 visit encounters for HIV care. The clinicians providing adherence assessment and education were two physicians, three nurse practitioners (NP), a registered nurse (RN) and a pharmacist. This group is reasonably believed to constitute a representation of the “average” specialist clinician treating HIV patients.

Three types of occasions for adherence education were observed. The first occasion for education is when planning to start a regimen. This may include discussions in visits prior to the actual prescription. The second occasion is at follow up, to monitor adherence and
repair any problems. The third is when a regimen is changed (all or part). Adherence education was more formalized for the new patient, or for the patient facing a significant regimen change. For patients already on ART for some time (months, years), the assessments focused on most of the major areas discussed by Golin et al. (2004), but with less emphasis on touching each point outlined by that group. The assessments tended to follow a model similar to that used in medical history taking, for example: clinicians often asked a screening question such as “Are you taking all of your meds ok?” Any equivocation would prompt further questions, e.g.: “Are you taking your Combivir with food?” or “Is it the taste of the Norvir that’s keeping you from taking it?” and so on, until a “diagnosis” of the adherence issue was established.

During the observations, clinicians missed some features of adherence education outlined by Golin, et al. (2004) in some visits. The assessment of adherence was sometimes approached in very different ways by different clinicians. This observation was recorded in all the regional clinics examined. Since both the control group and the experimental group will continue visiting their clinicians as scheduled, this SOC will be common to both groups.

The independent variable: the intervention protocol. The intervention consisted of three CBT sessions. The first session was designed to impart the basic therapeutic thrust of CBT which includes using thoughts to frame the experience and reinforce an internal sense—or locus—of control (A. T. Beck, 1976; J. S. Beck, 1995; Kalichman, 1995), and to discuss individual participant concerns, symptoms, etc. The cognitive piece of CBT was focused on assessing those concerns, and on working with the patient to establish a knowledge base about the purpose of the encounters. This teaching did not focus on knowledge about ART. That had already been done by the treating clinician, nurse, or pharmacist in a medical
setting. Rather, the purpose of this encounter was to inquire about perceived psychosocial limitations, how symptoms were being experienced, and their meaning to participants. Perceived limits to adherence, anxiety about medication taking, and other treatment-related issues were primary (K. Bakke-Friedland, personal communication, April 21, 2006). The session content is detailed in the following sections. Participants received reminders about appointments with the behavioral interventionist (BI) by telephone call to a number of their choice. The PI made all such contacts.

**Timing of the first session.** In participants assigned to the experimental group this first visit was planned to occur within two weeks of assignment. This was to allow for scheduling that would be convenient to participants, but assure that they also moved along at the same pace in the study as those participants in the control group.

**Detail: the first visit.** This was an introductory session. The items below were interspersed throughout the session, but are listed below in their approximate order of address within the session:

- CBT, its relevance to adherence.
- Introduction, and getting to know the participant, 10 minutes
- Self-defeating thinking, 12 minutes
- How automatic thoughts affect our mood and behaviors, 12 minutes
- Participant personal sharing, 10 minutes
- Plan for following sessions, 6 minutes

**Timing of the second session.** The second visit was scheduled about three to four weeks after the first session.
**Detail: the second visit.** This was designed to begin to implement the CBT strategies. Format was similar.

- Review and update with the participant by the behavioral interventionist (BI), 10 minutes
- Introduction to progressive muscle relaxation (PMRT), 10 minutes
- Coached session of PMRT, 15 minutes, (recorded)
- Questions and personal sharing, 10 minutes
- Plans for next session, 5 minutes

The PMRT session was recorded, and each participant was given a compact disk (CD) with the session for use in private practice sessions at home or elsewhere. No restrictions were placed on how often or where they could listen and practice. It was suggested they use the practice CD daily or at least several times a week.

*Progressive muscle relaxation training.* This involves the coached tensing and relaxation of groups of muscles. The tensing helps focus the person’s attention to the area. The person is then coached to relax the muscles just tensed. The original procedure could require 30-45 minutes (Bernstein & Borkovec, 1973). Later variations have been adapted to require as little as a few moments to several minutes to 20 minutes or more (Schweitzer & Miller, 2005). Bernstein and Borkovec offer very clear guidelines for PMRT. The present study modified these conditions. In this study we used the “seven muscle group” procedure (Bernstein & Borkovec, 1973, Chapter 7), as this was felt to provide a reasonably thorough session while preserving time. It requires 10-12 minutes. It was judged that participants should to be able to use PMRT as often as necessary, and that brevity could contribute to more frequent use. No literature was found that contradicted such an assumption.
Timing of the third session. The third session followed the second session by about three to four weeks.

Detail: the third session. This was designed to move the control of the techniques to the participant, review and follow up on any issues during the interim.

- Review and update with the participant by the BI, 10 minutes
- Introduction to guided imagery (GI), and exploration of participant imagery models, 10 minutes
- Coached session of GI, 15 minutes
- Disengagement, 15 minutes

Guided imagery. GI is a technique in CBT, and is the use of live coaching to help patients develop assistive, positive, or otherwise motivational imagery. Alternatively, the imagery may be relaxing and anxiety-relieving, or may be intended to force vicarious contact with feared events for the purpose of confronting unpleasant thoughts and then reframing them. The coaching of imagery is inspired in its development by the patient and how he symbolizes his world, but is guided by the therapist (J. S. Beck, 1995).

Although effect sizes are moderate (.50), PMRT and GI have been found to be effective in the management of similar symptom clusters (nausea, anxiety, etc.) associated with antineoplastic therapy (Burish, et al., 1987; Burish & Tope, 1992; Carey & Burish, 1987; Simonton, Matthews-Simonton, & Sparks, 1980), and were believed to be reasonable choices to begin exploring CBT in patients with HIV who are undergoing ART.

Duration and Personnel
All sessions were scheduled for 50 minutes, the industry-standard counseling session (Kathrine Bakke-Friedman, personal communication, June 16, 2006). All CBT intervention sessions were administered by a Pennsylvania-licensed psychologist.

Safety Issues Relative to CBT

During CBT sessions, it was considered possible that some participants might experience psychic discomforts related to specific concerns, and could include:

- Expressions of suicidal ideation
- Expressions of harm toward others
- Hallucinations, other manifestations of psychosis
- Unpleasant memories of suppressed events such as rape, battery, other forms of abuse
- Undiscovered psychological pathology that emerges during training sessions
- Any behavior, expression, or other event that, in the opinion of the therapist, should prompt an evaluation, as detailed in the next paragraph

Such events would prompt the primary investigator (PI) and the BI to discuss disposition of such participants. The plan for such events was that participants would be offered referral to inpatient or outpatient services, as appropriate, based on the clinical judgment of the team, in consultation with the participant’s treating clinician. Participants were advised prior to entry that such referral was not part of the study would be pursued within their ordinary treatment channels. (All patients of Ryan White-funded HIV services are covered in some way for such professional services for mental health. This does not rely on specific insurance plans, although such plans may be used to pay for mental health services.) All study participants were evaluated by the PI prior to entry for access to mental
health services. Participants were advised that they could withdraw at any time without penalty.

Other issues that could come to the attention of the PI or research team and demand reconsideration of further participation included:

- Hospitalization for opportunistic infection or other cause (e.g., myocardial infarction): termination of participation: if hospitalization would exceed one week
- Any opportunistic infection not requiring hospitalization (additional burden of medications or procedure may make orderly follow up impossible): re-evaluation of participation
- Symptoms such that a participant withdraws from ART: termination of participation
- Relapse of substance abuse behavior that interferes with participation in study visits: termination of participation if behavior is associated with missing any study visit

Brief hospital stays, a single episode of substance abuse followed by renewed abstention, or other relatively minor events were not considered to be reasons to discontinue participation, if he/she wished to continue. Antiretroviral therapy is often continued in such circumstances. It was reasonable to consider that the CBT intervention could even contribute to continued use of ART by patients experiencing such short term difficulties.

**Procedures for Data Collection**

After consent and randomization, each participant was provided with the first set of measurement tools and allowed time to complete them while waiting during the medical visit. In a few cases, time constraints made it necessary for the participant to complete and return the measurement tools to the researcher via a self-addressed, postage paid envelope. In all cases, participants were provided with verbal instructions read from the instrument. The
instructions were also available for the participant to read later if needed. Participants in the control group were asked to complete and return the measurement tools at specific time points. Thus, two or three sets of measurement tools were given to the control group participants after informed consent was obtained.

Each set of measurement tools included a symptom VAS, an SF-36, and an adherence tool (both VAS and 3-day recall). A SERM diary was also include in each set. Each tool, in addition to including instructions on use, was individually marked with the participant number, the measurement number, and the date completed. Sets of measurement tools given to the control group participants for completion at end of 30-, 60-, and 90-days, were further marked with the specific dates to be completed. In addition, each set of tools was color coded using tinted paper, to provide further clarity. Participants in the experimental group also received calendars with instructions on how to record practice sessions of PMRT (for measurements T3 through T4). However, these were not provided until they had actually attended the second session, and were individually dated for each participant. As a rule, all instruments’ instructions were discussed with participants.

There were four planned measurement events. The planned timing is shown in the scheme in Figure 3.1. In planning, it was believed that scheduling could conform somewhat closely to this scheme. In practice, these times were difficult to adhere to. More on this is discussed in later chapters. As was noted, telephone reminders were used frequently, both to remind control group participants to complete their measurements, and to remind experimental group participants to attend their meetings with the BI, as well as to remind them to complete their final surveys.
Participants entering the study were measured at $T_1$, study entry, and then again at $T_2$ (1 month into the subject’s participation in the study), $T_3$ (two months into the study) and $T_4$ (three months into the study, at its end). The measurements in the experimental group were to be timed similarly, although getting measurements \textit{before} the intervention visit, even immediately before, was considered paramount, as it was believed that measurements immediately after the intervention visit would be artificially improved (lower symptom scores, higher SF-36 scores) because of “priming” recollections with a recent pleasant experience (the intervention visit). The data collection plan is shown in Table 3.2.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{study_scheme.png}
\caption{Study Scheme.}
\end{figure}

\textit{Notes:} $T_1$: Time 1 (study start); $T_2$: Time 2 (1 month); $T_3$: Time 3 (2 months); $T_4$ Time 4 (study exit). I1: Intervention 1 (scheduled within 2-4 weeks of study start); I2: Intervention 2 (scheduled 2-4 weeks after first intervention); I3: Intervention 3 (scheduled 2-4 weeks after second intervention).
Table 3.3

Data Collection Plan

<table>
<thead>
<tr>
<th>Group</th>
<th>Study Start (Time 1)</th>
<th>1 Month (Time 2)</th>
<th>2 Months (Time 3)</th>
<th>Study Exit (Time 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>E</td>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>Measures</td>
<td>VAS</td>
<td>SF36</td>
<td>VAS</td>
<td>SF36</td>
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<td>VAS</td>
<td>SF36</td>
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<td>SERM</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>VL</td>
<td></td>
<td></td>
<td>VL</td>
<td></td>
</tr>
<tr>
<td>How collected</td>
<td>In person</td>
<td>In person</td>
<td>Mail (Before session)</td>
<td>Mail (Before session)</td>
</tr>
</tbody>
</table>

Note. C = control group; E = experimental group; VAS = visual analogue scales for nausea, pain, fatigue, anxiety; SF36 = Short Form-36; SERM = side-effect reducing medication diary sheet; PRAC = practice diary calendar; CD4 = lymphocyte counts; and, VL = serum virus level.

Ethical Considerations

Approvals. Institutional Review Board (IRB) approval was obtained from Duquesne University and from Penn State University College of Medicine (Hershey, PA). Informed consent (Appendix D, approved by both IRBs) was presented to subjects after they expressed an interest in the study but before randomization. Participants and clinicians were reminded that changes in medical regimens as deemed necessary, as well as the use of SERM, should proceed as they normally would, and was believed would reflect real-world demands of ART as well as supports participants’ safety. The consent form was explained to each participant, and each was given ample time to read the form. The investigator completed National Institutes of Health Human Subjects Protection Education for Research Teams on February 6, 2004, on file with Duquesne University School of Nursing. Penn State employs a proprietary computer-based tutorial that concerns human subjects’ protection, and this was completed by

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the PI as part of the IRB approval process at that institution, and is on file with the Human Subjects Protection Office in the College of Medicine.

**Health Insurance Portability and Accountability Act (HIPAA) and data security.** Approvals for information security were obtained during the Duquesne University IRB approval process. At the beginning of their participation individuals were assigned a code number, sequentially generated from “01”. All materials related to the participant, such as mailed surveys, displayed only that number, and no name. Data files displayed the number only. The only place names and numbers appeared together on any document or file was in the data folders, kept in a locked cabinet at the PI’s university office. The number was generated at the same time as informed consent was obtained and followed each participant throughout the study. Once used, numbers were discarded if a participant left the study; thus all numbers were unique.

Initially, mail communications were thought to be a potential security concern (since a name would be on each envelope); however, all participants agreed to receive mail communications and did not express any special concern about that. Efforts were made to avoid using terms like “HIV” “AIDS” or “antiretroviral” on any printed materials (such as measurement instruments) and in phone messages/reminders.

A “master list” in Microsoft Excel contained no reference to the terms “HIV,” “CD4,” or any other health information, and served to link numbers with names, progress in the study, and other tracking information. This was necessary to maintain the study, and the data were kept on removable a removable medium, not part of a laptop hard drive, and kept with the data folders, as well. The BI completed a confidentiality agreement (Appendix E).
All identifiable data including raw data files and consents was destroyed at the end of the study (approval of dissertation and final filing of electronic dissertation).

**Payment to participants.** Participants were paid $10 for each set of surveys completed, to help defray costs of transportation, childcare or other inconvenience. Payment was the same regardless of whether a participant was in the control or experimental group. Cash was paid during in-person encounters. Checks were issued from a private account for mailed surveys.

**Data Analysis**

The independent variable under study is the introduction of the experimental intervention. The dependent variables are summarized in Table 3.3. These include potential confounding variables. Descriptive statistics were performed, and the groups examined at T1 for equivalence. The data were also examined for normal distribution of scores and variances between groups.

**Statistical tests.** The study examined three hypotheses, one directional and two non-directional, and also considered an array of potential confounders or covariances (e.g., SERM use). The intervention and measurements was planned to occur over three months. Multiple analysis of variance (MANOVA) and repeated measures analysis of variance (RM-ANOVA) were considered, as these would account for between-group differences, within-group differences over time, and the effects of variables on one another, as well as reduce the likelihood of Type I error. Use of these tests, however, depends on the data meeting criteria for parametric testing and would have required a very large sample size (Field, 2009, P. Ricci, personal communication, September 11, 2009). A study designed as a proof-of-concept trial would not submit to these tests, given the small sample size. In addition, Polit
and Beck (2004) and Field (2009) argue that multiple ANOVAs do not truly test the effects of multiple variables among groups, they merely repeat the same analysis with different variables.

Table 3.4
Dependent and Control Variables

<table>
<thead>
<tr>
<th>Variable &amp; number of dimensions</th>
<th>Measure and Scale</th>
<th>Analysis of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea 3 dimensions</td>
<td>VAS 0-100 mm</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Pain 3 dimensions</td>
<td>VAS 0-100 mm</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Fatigue 3 dimensions</td>
<td>VAS 0-100 mm</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Anxiety 3 dimensions</td>
<td>VAS 0-100 mm</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Physical Function</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Role Physical</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>General Health</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Vitality</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Social Function</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Role Emotion</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Mental Health</td>
<td>SF-36 0-100 normative</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Adherence</td>
<td>VAS 0-100 mm</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Adherence</td>
<td>3-day recall</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Doses taken/Doses Prescribed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load</td>
<td>Log 10</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>CD4</td>
<td>Absolute count</td>
<td>Primary hypothesis</td>
</tr>
<tr>
<td>Doses of SERM</td>
<td>Days in period/Doses taken (Arithmetic average)</td>
<td>Control variable</td>
</tr>
<tr>
<td>Times CBT practices</td>
<td>number of participant-initiated practice CBT sessions</td>
<td>Control variable</td>
</tr>
</tbody>
</table>

Note: VAS = visual analogue scales for nausea, pain, fatigue, anxiety; SF36 = Short Form-36; SERM = side-effect reducing medication diary sheet; CD4: lymphocyte counts; the number of dimensions includes a VAS for each of level of the symptom in general, the worst experience of that symptom, and the average duration of the symptom, over the prior month.
factors without the ability to examine the effect of simultaneity that actually does occur with multiple independent variables (e.g., our “control variables”, participant attributes). Doubly-multivariate analysis is another method to test several related, dependent measures, repeated at fixed time points. However, the number of dependent variables cannot exceed the number of participants in that method (P. Ricci, personal communication, September 14, 2009), which was the case in this study. Parametric testing rests on assumptions of independence, equal variances, and normality of scores. Because these could not be assumed until the data were actually analyzed, post hoc, non-parametric testing was also planned.

Hypotheses of extent of change. This study hypothesized that changes (effect sizes) would be at least one standard deviation (SD) of 20 mm on the VAS. Various ranges of effect size for various psychological interventions in oncology symptom management are .17 to .64 (Meyer & Mark, 1995), and .31 to .49 (Tatrow & Montgomery, 2006). An effect size of .50 could be expected. However, in other studies limited to using VAS as a measurement tool, effects sizes were much larger, perhaps because of the sensitivity of VAS to changes in symptom levels (Gift, 1989; Grant, et al., 1999). Several such studies are summarized in the next paragraph. A change of 20mm (20%) has been considered a clinically significant change in other studies (Nusstein, Steinkruger, Reader, Beck, & Weaver, 2006; Syrjala, Donaldson, Davis, Krippes, & Carr, 1995; Wang, Belza, Thompson, Whitney, & Bennett, 2006),

Power analysis. The study proposed to enroll 15 per study group.

Using the formula:

$$ES = \frac{\mu_1 - \mu_2}{\sigma}$$
Using a hypothetical average score of 50 mm, the experimental change would be assumed as a mean of 30 mm.

\[
ES = \frac{50 - 30}{\sigma}
\]

\[
1.00 = \frac{20}{20}
\]

Using an effect size of 1.00 we can calculate that 15 participants in each group would provide a power of .80. The study aimed to recruit 15 participants for each group (K. Kjelrulff, personal communication, July 3, 2007; Lenth, 2006; Lipsey, 1990)

**Level of significance.** One-tailed testing with the significance level set at .05 was planned for the first, directional hypothesis concerning VAS symptom scores and SF-36 scores, and two tailed testing was selected for the non-directional hypotheses concerning adherence and CD4 counts/viral loads. The use of a level of .05 is a common level of significance for studies of psychobehavioral interventions in nursing and psychology studies (Polit & Beck, 2004).

**Software.** The analysis used version 16.0.1 of SPSS\textsuperscript{TM} for the overall analysis. Scoring for the SF-36 was done on Microsoft Excel 2007\textsuperscript{TM}, with author-programmed formulae based on the scoring algorithms in Ware, Kosinski, & Gandek (2005).

**Summary**

This was a randomized, controlled clinical trial that planned to recruit 30 participants (approximately 15 in each arm). Each group of HIV-infected participants would receive the standard of care (adherence education). The experimental group would meet with the BI, who would deliver three sessions of CBT with an emphasis on participant-practicable techniques such as PMRT and GI, chosen for their demonstrated ability to reduce arousal, and shift locus
of control internally. This was done to examine whether or not experimental group participants would score lower on VAS of nausea, pain, fatigue, and anxiety, and whether the intervention would have any effect on adherence, CD4 or viral load. Males and females 18 or older were recruited from an infectious disease clinic. Participants had to be on ART for any duration, and to have one or more of the symptoms being measured. In addition, general health measures, adherence to medications, SERM use, and laboratory data were to be collected at four time points over three months. Planned analyses included repeated measures ANOVA, with non-parametric testing used for the post hoc analyses.
Chapter 4

Results and Data Analysis

This chapter reports the findings, and begins with a report of the sample that was recruited. The final sample is described and the composition of the experimental and groups follows. The statistical analysis is introduced. Finally, the results and analysis of data are organized according to hypotheses tested.

Recruitment and Study Completion

Recruitment took place over an eight month period from September 16, 2008 to June 1, 2009. The target enrollment was 30, with an estimated number per group of 15. Final enrollment was 33, with 9 in each group completing the study. During the recruitment period, 384 individuals were screened by clinic staff, and 57 were approved for recruitment. This captured 15% of the clinic attendance. Of these, 33 agreed to participate. No specific data were collected on why potential participants declined participation but the most common reasons noted were disinterest and/or lack of symptoms. Table 4.1 displays details about the participants as they progressed to the end of the study. A total of 18 (55%) of the enrolled participants completed the study; 15 or 45% of those enrolled did not complete the study. Participation of those listed as “Suspended” was finally discontinued by the investigator because the intervention became unavailable due to the loss of the behavioral interventionist. This was because of unexpected and personal reasons.

No data were collected on why participants left the study, beyond the reasons stated in Table 4.1. Participants lost to follow-up (LTF) were contacted more than eight times on average, and generally for 30 days before no further contact was attempted. In most cases, the staff
was unable to supply any additional information on why such participants could not be contacted.

Table 4.1
Summary of Enrollees and Withdrawals

<table>
<thead>
<tr>
<th>Group</th>
<th>$N$ enrolled</th>
<th>$N$ completing</th>
<th>% Completing</th>
<th>Reasons for Leaving the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>9</td>
<td>75</td>
<td>LTF 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>21</td>
<td>9</td>
<td>42</td>
<td>LTF 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Scheduling problems 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medical 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Died 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Incarcerated 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suspended 3*</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>18</td>
<td>55</td>
<td>15</td>
</tr>
</tbody>
</table>

Note. *Suspended when the enrollment was halted. LTF = lost to follow-up.

Figure 4.1 Summary of Recruitment and Retention

Number of clinic patients screened by staff: 384
Number of clinic patients approached for recruitment: 57
Number of patients consented to study: 33 (58%)
Number of participants who completed the study: 18 (55%)
Not consenting: 24 (42%)
Not completing: 24 (45%)
Description of the Sample

Participants who completed the study are described in Tables 4.2 and 4.3. The sample was predominantly Caucasian males, with the exception of one Caucasian female participant. Experimental designs assume that randomization will produce groups that are comparable. This study used a randomized design until 29 participants were enrolled. At this time losses to follow-up already approached approximately 27% (attempts to contact recent lost participants were continuing), and assignment was changed to a stratified randomized design. The remaining four enrollees were all assigned to the experimental group, however none completed the study and thus, by default, a true randomized design was preserved in the final data set. A \( t \)-test of between group differences at baseline suggests that the groups were not significantly different. The majority of participants were white males.

Table 4.2

Demographic Composition of the Sample

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>94.4</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>Caucasian</td>
<td>15</td>
<td>83.3</td>
</tr>
<tr>
<td>Caucasian Hispanic</td>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>11.1</td>
</tr>
</tbody>
</table>
Table 4.3

Descriptive Statistics of the Total Sample (N=18).

<table>
<thead>
<tr>
<th>Statistic</th>
<th>N</th>
<th>Range</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
<th>Variance</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>18</td>
<td>16</td>
<td>40</td>
<td>56</td>
<td>46.8</td>
<td>4.2</td>
<td>17.4</td>
<td>.67</td>
</tr>
<tr>
<td>ART # of Weeks</td>
<td>18</td>
<td>467</td>
<td>13</td>
<td>480</td>
<td>200.2</td>
<td>160.5</td>
<td>25772.5</td>
<td>.58</td>
</tr>
<tr>
<td>Starting CD4</td>
<td>13</td>
<td>1241</td>
<td>121</td>
<td>1362</td>
<td>544.2</td>
<td>352.2</td>
<td>124069.5</td>
<td>1.10</td>
</tr>
<tr>
<td>Starting VL</td>
<td>18</td>
<td>147</td>
<td>0</td>
<td>147</td>
<td>58.6</td>
<td>42.9</td>
<td>1838.9</td>
<td>-.038</td>
</tr>
<tr>
<td>Start Log10VL</td>
<td>18</td>
<td>2.2</td>
<td>0.0</td>
<td>2.2</td>
<td>1.4</td>
<td>.9</td>
<td>.79</td>
<td>-1.05</td>
</tr>
<tr>
<td>Valid N</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Completeness of data. The demographic data were 100% complete. More than 90% of the surveys were completed and returned. Of the surveys that were collected >95% of the items were completed; that is, the VASs (symptom scores and adherence), and the items on the SF-36. About 85% of the SERM-use diaries were returned, many blank, and blank diaries were counted as “no SERM used.” Complete sets of laboratory data were missing on all with the exception of six participants, and many had neither beginning nor ending reports. The most common reason for missing laboratory data was that the participant had not reported to a laboratory for the sample to be drawn. The second most common reason (only two cases) was that the laboratory itself had a problem with the sample (e.g., test not run, sample ruined, etc.). There were six complete observations for CD4 and viral load (VL), with both study entry and study exit values reported. The standard deviations (SD) for CD4 and VL for these pairs of observations were high, and given the low number of complete sets of laboratory data.
measures, imputation analysis with an expectation-maximization (EM) algorithm was used to replace missing values with plausible ones. Thus several values in the laboratory data were *imputed* from the data that was available, based on estimates of likelihood. Given the low number of participants, this imputation of laboratory values had to be done for statistical power when analyzing that data. (P. Ricci, personal communication, September 20, 2009).

In analyzing for differences between the groups at the start of the study, imputation analysis did not change results for sex, race/ethnicity, age, and ART duration in weeks. Imputation analysis did change results for CD4, viral load count and viral load by log_{10}. The groups were compared at study start, both before and after the imputation correction was applied to the laboratory data. As shown in Table 4.4, the experimental and control groups were equivalent at the beginning of the study.

Table 4.4

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Between Groups Sig. (2-tailed)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>.347</td>
<td>NS</td>
</tr>
<tr>
<td>Race/Ethnic</td>
<td>.313</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>.957</td>
<td>NS</td>
</tr>
<tr>
<td>ART Weeks</td>
<td>.838</td>
<td>NS</td>
</tr>
<tr>
<td>Starting CD4</td>
<td>.981</td>
<td>NS</td>
</tr>
<tr>
<td>Starting VL</td>
<td>.328</td>
<td>NS</td>
</tr>
<tr>
<td>Start Log10VL</td>
<td>.517</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Note.* Results are based on data set with imputation analysis, reflected in the clinical measures for which there were missing data. ART: antiretroviral therapy. CD4: CD4 lymphocyte absolute count. VL: viral load. Log10VL: VL in log10. NS: not significant.
Analysis of the Sample for Statistical Testing

Using Lenth’s (n.d.) Power Analysis for ANOVA Designs (Java applet) the following numbers of participants are suggested for effects sizes of .50, .75, and 1.00: eight, four, and two, for each group, respectively. Lenth notes that this applet is limited in its ability to calculate samples sizes for multiple-measure designs. This limitation was addressed by taking each measurement interval as a “level” of measurement in the factor table, the number of participants using Lenth’s applet describes eight levels in all. Hence for the number of subjects in this study an effect size of .1.00 size was required to achieve a power of .80. As was noted in Chapter Three, the study’s power analysis was originally based on a clinically significant change of 20mm on symptom VAS scores, and on 30 participants completing the protocol. Of the 33 participants originally enrolled in the study, only 18 completed the study. Enrollment was halted due to a lack of additional eligible patients. Some pairs of laboratory data were missing. Imputation was performed to create a data set that would respond to analyses. The final data set did not fully meet criteria for parametric testing. There was no random sampling, and values for skewness and kurtosis exceeded suggested limits. The planned comparison for this study was based on parametric testing. For parametric testing to be valid there are several criteria that should be met. The data must be normally distributed, display homogeneity of variance, and be independent (Field, 2009). Frequency analysis was performed on all of the variables in the sample including computation of skewness and kurtosis. To summarize the results of this analysis, mean skewness and mean kurtosis are reported in Table 4.5 for each of the four measurement points for the symptom scores measured by a VAS. Values of skewness and kurtosis close to zero suggest more normal distribution of scores. In smaller samples, values of skewness and kurtosis were converted to
z-scores; those not exceeding a SD of 1.96 generally conformed to normality. Note that in this sample, z-scores for kurtosis generally exceeded 1.96; however, in a sample this small, even values that somewhat exceed 1.96 (2.0 - 2.5) do not necessarily stamp the sample as non-normal (Field, 2009).

Table 4.5

Symptom Scores: Mean Skewness and Kurtosis

<table>
<thead>
<tr>
<th>Symptom measures</th>
<th>Average z-score Skewness</th>
<th>SD</th>
<th>Average z-score Kurtosis</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>-0.03</td>
<td>1.69</td>
<td>-0.40</td>
<td>2.11</td>
</tr>
<tr>
<td>T2</td>
<td>0.14</td>
<td>1.89</td>
<td>-0.39</td>
<td>2.35</td>
</tr>
<tr>
<td>T3</td>
<td>-0.09</td>
<td>2.29</td>
<td>0.27</td>
<td>2.43</td>
</tr>
<tr>
<td>T4</td>
<td>-0.28</td>
<td>1.78</td>
<td>-0.10</td>
<td>2.39</td>
</tr>
</tbody>
</table>

Note. SD: standard deviation; T1: time 1, at study entry; T2: time 2, measurement at 1 month, or just prior to the first visit with the behavioral interventionist; T3: time 3, at 2 months, or just prior to the second visit with the behavioral interventionist; T4, time 4, at 3 months and study completion.

Regarding the assumptions of parametric testing, it can be said that the groups were independent, that some variances between the groups were not equivalent (sex, race/ethnicity, ART duration, starting VL count), and that the distribution of symptom measurement scores did not achieve normality.

Hypothesis Testing

There were three hypotheses:

1. Participants who received the cognitive-behavioral therapy (CBT) intervention would report a reduction in side effects, compared to participants who only received the standard of care (SOC).
2. Participants who received the CBT intervention would show a difference in adherence compared to those who only received the SOC.

3. Participants who received the CBT intervention would show a difference in CD4 and VL compared to those who only received the SOC.

The first hypothesis was analyzed in two parts. First, side effects data from the third (T3) and fourth (T4) measurements of nausea, pain, anxiety and fatigue are reported. Second, general health data from the third (T3) and fourth (T4) measurements are reported and examined in correlation with side effects. The symptom variables are described by the terms used on the visual analogue scales for symptom measurements. As in Table 3.3, variables are described in terms of the dimension of the symptom, e.g., “usual nausea” or “worst pain.” When discussing symptoms as general concepts, terms like “nausea” and “pain” are used.

**Hypothesis One: Side Effects.** The null hypothesis assumed that there would be no differences between the groups with respect to side effect symptoms. For this study, the null hypothesis was rejected in favor of the alternate hypothesis. The first hypothesis assumed that participants who received the CBT intervention would report a reduction in side effects, compared to participants who only received the SOC. Parametric testing was planned, but was rejected at this stage because the data did not meet criteria for parametric testing. Mann-Whitney U and Wilcoxon rank sum testing were performed to determine between-group differences on both the VAS symptom data and the SF-36 data for T3 and T4. The results appear in Tables 4.6 and 4.7. Analysis of the means between groups did not show radical differences between symptom scores before and after imputation analysis was performed.

Tables 4.6 and 4.7 display the results of the Mann-Whitney U exact test. One-tailed testing for significance was used. All of these results demonstrated moderate effect sizes.
ranging from .41 to .52. Usual fatigue scores in the experimental group \((\text{Median} [\text{Mdn}] = 42.00)\) were significantly lower than in the control group \((\text{Mdn} = 60.00)\) at T3, \(U = 12.50, z = -2.01, r = -.47, p < .05\). Worst fatigue scores in the experimental group \((\text{Mdn} = 59.00)\) were significantly lower than in the control group at T3 \((\text{Mdn} = 73.00), U = 15.50, z = -1.16, r = - .40, p < .05\). No significant differences between the groups resulted at T1 and T2.

Duration of nausea scores in the experimental group \((\text{Mdn} = 17.00)\) were significantly lower than in the control group \((\text{Mdn} = 36.00)\) at T4, \(U = 18.00, z = -1.73, r = -.41, p < .05\). Imputed means and variances are not radically different from true means and variances. Thus, the analysis changed little with imputation. Usual nausea scores in the experimental group \((\text{Mdn} = 11.95)\) were significantly lower than in the control group \((\text{Mdn} = 32.00)\) at T4, \(U = 21.00, z = -1.72, r = -.41, p < .05\) only when the data were analyzed after imputation. There was trend toward lower usual nausea scores in the experimental group \((p = .08)\) when the raw data were analyzed. The results of both analyses are shown in Tables 4.6 and 4.7

**Hypothesis One: General Health.** The SF-36 was used to look at general health measures that could be affected by symptoms. For example, if nausea were a problem, it is reasonable to expect that various health domains such as vitality, social role and others could be affected. Moreover, the SF-36 measures domains, such as Bodily Pain that corresponds to pain as measured by VAS. There were no significant differences between the experimental and control groups.

To summarize, the experimental group reported significantly lower scores for nausea and fatigue over the course of their involvement with the study after having been exposed to the treatment intervention compared to the control group that received only the SOC.
Table 4.6

Test of Hypothesis 1: Differences Between Groups at T3 and T4 Before Imputation

<table>
<thead>
<tr>
<th></th>
<th>Mann-Whitney U</th>
<th>Z</th>
<th>Exact Sig. (1-tailed)</th>
<th>Point Probability</th>
<th>Effect size (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time 3: 2 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual Nausea</td>
<td>28.000</td>
<td>-.374</td>
<td>.367</td>
<td>.017</td>
<td></td>
</tr>
<tr>
<td>Worst Nausea</td>
<td>24.000</td>
<td>-.801</td>
<td>.223</td>
<td>.012</td>
<td></td>
</tr>
<tr>
<td>Duration Nausea</td>
<td>23.500</td>
<td>-.854</td>
<td>.209</td>
<td>.015</td>
<td></td>
</tr>
<tr>
<td>Usual Pain</td>
<td>20.000</td>
<td>-1.217</td>
<td>.126</td>
<td>.021</td>
<td></td>
</tr>
<tr>
<td>Worst Pain</td>
<td>18.500</td>
<td>-1.377</td>
<td>.091</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>Duration Pain</td>
<td>26.000</td>
<td>-.584</td>
<td>.293</td>
<td>.016</td>
<td></td>
</tr>
<tr>
<td>Usual Anxiety</td>
<td>30.500</td>
<td>-.106</td>
<td>.470</td>
<td>.022</td>
<td></td>
</tr>
<tr>
<td>Worst Anxiety</td>
<td>30.000</td>
<td>-.159</td>
<td>.459</td>
<td>.041</td>
<td></td>
</tr>
<tr>
<td>Duration Anxiety</td>
<td>31.000</td>
<td>-.053</td>
<td>.500</td>
<td>.041</td>
<td></td>
</tr>
<tr>
<td>Usual Fatigue</td>
<td>12.500</td>
<td>-2.013</td>
<td>.022*</td>
<td>.003</td>
<td>-.47</td>
</tr>
<tr>
<td>Worst Fatigue</td>
<td>15.500</td>
<td>-1.695</td>
<td>.047*</td>
<td>.005</td>
<td>-.40</td>
</tr>
<tr>
<td>Duration Fatigue</td>
<td>17.500</td>
<td>-1.485</td>
<td>.075</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td><strong>Time 4: 3 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual Nausea</td>
<td>21.000</td>
<td>-1.444</td>
<td>.080**</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Worst Nausea</td>
<td>28.000</td>
<td>-.771</td>
<td>.233</td>
<td>.015</td>
<td></td>
</tr>
<tr>
<td>Duration Nausea</td>
<td>18.000</td>
<td>-1.733</td>
<td>.043*</td>
<td>.005</td>
<td>-.41</td>
</tr>
<tr>
<td>Usual Pain</td>
<td>30.500</td>
<td>-.530</td>
<td>.313</td>
<td>.020</td>
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<tr>
<td>Worst Pain</td>
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<td>-.096</td>
<td>.472</td>
<td>.019</td>
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<tr>
<td>Duration Pain</td>
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<td>-.674</td>
<td>.263</td>
<td>.015</td>
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<td>Usual Anxiety</td>
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<td>.034</td>
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<tr>
<td>Worst Anxiety</td>
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<tr>
<td>Duration Anxiety</td>
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<td>.155</td>
<td>.011</td>
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</tr>
<tr>
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<td>.017</td>
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<td>.014</td>
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</tr>
<tr>
<td>Duration Fatigue</td>
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<td>-.289</td>
<td>.398</td>
<td>.018</td>
<td></td>
</tr>
</tbody>
</table>

Note: * < or = .05 level of statistical significance. **Trend toward significance at .05 level. Z = z-score for calculation of effect sizes. Only effect sizes for significant results have been calculated.
Table 4.7

Test of Hypothesis 1: Differences between Groups at T3 and T4 After Imputation

<table>
<thead>
<tr>
<th></th>
<th>Mann-Whitney U</th>
<th>Z</th>
<th>Exact Sig. (1-tailed)</th>
<th>Point Probability</th>
<th>Effect size (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time 3: 2 months</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Usual Nausea</td>
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<td>-0.133</td>
<td>.456</td>
<td>.016</td>
<td></td>
</tr>
<tr>
<td>Worst Nausea</td>
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<td>-0.489</td>
<td>.324</td>
<td>.015</td>
<td></td>
</tr>
<tr>
<td>Duration Nausea</td>
<td>35.50</td>
<td>-0.444</td>
<td>.340</td>
<td>.016</td>
<td></td>
</tr>
<tr>
<td>Usual Pain</td>
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<td>-1.104</td>
<td>.149</td>
<td>.020</td>
<td></td>
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<td>Worst Pain</td>
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<td>.060</td>
<td>.006</td>
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<td>.323</td>
<td>.012</td>
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<td>.441</td>
<td>.019</td>
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<td>Worst Anxiety</td>
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<td>-0.309</td>
<td>.398</td>
<td>.033</td>
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</tr>
<tr>
<td>Duration Anxiety</td>
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<td>-0.044</td>
<td>.500</td>
<td>.034</td>
<td></td>
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<td>Usual Fatigue</td>
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<td>-0.52</td>
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<td>.002</td>
<td>-0.46</td>
</tr>
<tr>
<td>Duration Fatigue</td>
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<td>-1.327</td>
<td>.099</td>
<td>.008</td>
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</tr>
<tr>
<td><strong>Time 4: 3 months</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Usual Nausea</td>
<td>21.00</td>
<td>-1.723</td>
<td>.045*</td>
<td>.005</td>
<td>-0.41</td>
</tr>
<tr>
<td>Worst Nausea</td>
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<td>-1.105</td>
<td>.143</td>
<td>.010</td>
<td></td>
</tr>
<tr>
<td>Duration Nausea</td>
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<td>.024*</td>
<td>.003</td>
<td>-0.47</td>
</tr>
<tr>
<td>Usual Pain</td>
<td>30.50</td>
<td>-0.883</td>
<td>.200</td>
<td>.013</td>
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</tr>
<tr>
<td>Worst Pain</td>
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<td>.492</td>
<td>.017</td>
<td></td>
</tr>
<tr>
<td>Duration Pain</td>
<td>29.00</td>
<td>-1.017</td>
<td>.164</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td>Usual Anxiety</td>
<td>37.00</td>
<td>-0.309</td>
<td>.398</td>
<td>.033</td>
<td></td>
</tr>
<tr>
<td>Worst Anxiety</td>
<td>29.00</td>
<td>-1.015</td>
<td>.170</td>
<td>.021</td>
<td></td>
</tr>
<tr>
<td>Duration Anxiety</td>
<td>29.00</td>
<td>-1.017</td>
<td>.164</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td>Usual Fatigue</td>
<td>35.50</td>
<td>-0.442</td>
<td>.342</td>
<td>.017</td>
<td></td>
</tr>
<tr>
<td>Worst Fatigue</td>
<td>31.50</td>
<td>-0.796</td>
<td>.225</td>
<td>.013</td>
<td></td>
</tr>
<tr>
<td>Duration Fatigue</td>
<td>40.00</td>
<td>-0.044</td>
<td>.491</td>
<td>.017</td>
<td></td>
</tr>
</tbody>
</table>

*Note:* * < or = .05 level of statistical significance. **Trend toward significance at .05 level. Z = z-score for calculation of effect sizes. Only effect sizes for significant results have been calculated.
Hypothesis Two. The second hypothesis predicted that participants who received the CBT intervention would show a difference in adherence compared to those who only received the SOC. The direction of such a difference was undetermined. Adherence was measured by a VAS (Giordano, et al., 2004) and by a three-day recall instrument (Chesney, et al., 2000). At three of the four measurement intervals, both measures were highly correlated. The data were non-normal, with both the VAS adherence scores and the 3-day recall scores skewed sharply to the right. Skewness changed little from when the data were examined in their raw state, and when the data were transformed using the sum of squares and natural logs. Participants were on ART an average of 200 weeks (SD 160.5) and had adherence rates approaching 100%. Adherence was high even at the study entry with mean adherence by the VAS of 93.4 (SD 10.86, range 70-100) and a 3-day recall of .89 (SD .17, range .67-1.00). Moreover, Levene’s tests of variances were not homogenous for means (necessary for parametric testing) \( p < .05 \) but were homogenous for medians \( p > .05 \) (either case is acceptable for non-parametric testing). Two-tailed tests of significance were used for this analysis. Between-group differences were non-significant and adherence rates were high for both the experimental and control groups during the course of the study. The null hypothesis was accepted.

Hypothesis Three. Participants who received the CBT intervention were expected to show a difference in CD4 and VL compared to those who only received the SOC. The direction of change was not hypothesized. The null hypothesis stated that there would be no difference between the groups with respect to CD4 and VL. For CD4 there were six complete observations for pre and post with the following means and SDs. Earlier it was noted that due to the paucity of laboratory data imputation analysis was used to generate plausible pairs of
Table 4.8

Correlations Between 3-day Recall and VAS for Adherence

<table>
<thead>
<tr>
<th>Measurement Interval</th>
<th>3DR – VAS</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Start</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1</td>
<td>.81</td>
<td>*p &lt; .01</td>
</tr>
<tr>
<td>1 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 2</td>
<td>.57</td>
<td>*p &lt; .05</td>
</tr>
<tr>
<td>2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 3</td>
<td>.98</td>
<td>*p &lt; .01</td>
</tr>
<tr>
<td>Study Exit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 4</td>
<td>.84</td>
<td>*p &lt; .01</td>
</tr>
</tbody>
</table>

Notes: 3DR: 3-day recall; VAS: visual analogue scale.

Figure 4.2  Weeks on ART at Study Entry, by Participant Number

Notes: ART: antiretroviral therapy. Actual values in weeks displayed in boxes.
Table 4.9

Participant-estimated Adherence by VAS, Non-parametric Testing, Group Differences

<table>
<thead>
<tr>
<th></th>
<th>Adherence VAS T1</th>
<th>Adherence VAS T2</th>
<th>Adherence VAS T3</th>
<th>Adherence VAS T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
<td>1.395</td>
<td>2.138</td>
<td>.549</td>
<td>3.220</td>
</tr>
<tr>
<td>df</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asymp. Sig.</td>
<td>.237</td>
<td>.144</td>
<td>.459</td>
<td>.073</td>
</tr>
</tbody>
</table>

Notes: Kruskal Wallis test, grouping variable by assignment. Asymp. Sig.: Asymptotic significance.

CD4 counts and viral loads. During preliminary analysis of the data the extent of missing data in this particular variable was observed, resulting in use of EM algorithm imputation to continue the analysis. One case with missing data for both CD4 and viral load in the experimental group was excluded. The imputed means and standard deviations were lower but the patterns of means were the same.

Table 4.10

Descriptive Statistics of Raw Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Range</th>
<th>Mean</th>
<th>SD</th>
<th>Variance</th>
<th>Skew</th>
<th>Kurtosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting CD4</td>
<td>13</td>
<td>121</td>
<td>1362</td>
<td>544.23</td>
<td>124069.53</td>
<td>1.14</td>
<td>1.14</td>
</tr>
<tr>
<td>Start Log10VL</td>
<td>13</td>
<td>1.7</td>
<td>2.2</td>
<td>1.92</td>
<td>0.11</td>
<td>0.26</td>
<td>3.29</td>
</tr>
<tr>
<td>Ending CD4</td>
<td>18</td>
<td>148</td>
<td>9999</td>
<td>2094.17</td>
<td>13303302.74</td>
<td>1.93</td>
<td>1.99</td>
</tr>
<tr>
<td>Ending Log10VL</td>
<td>18</td>
<td>.0</td>
<td>2.6</td>
<td>1.41</td>
<td>0.92</td>
<td>-0.86</td>
<td>-0.98</td>
</tr>
</tbody>
</table>

Note: CD4: CD4 count, VL: viral load.
Table 4.11

Descriptive Statistics: CD4 Means Compared Before and After Imputation

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Imputation Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting CD4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>524.33</td>
<td>223.031</td>
<td>6</td>
</tr>
<tr>
<td>Experiment</td>
<td>600.17</td>
<td>484.194</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>562.25</td>
<td>361.585</td>
<td>12</td>
</tr>
<tr>
<td>Ending CD4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>519.00</td>
<td>175.442</td>
<td>6</td>
</tr>
<tr>
<td>Experiment</td>
<td>579.50</td>
<td>424.900</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>549.25</td>
<td>311.533</td>
<td>12</td>
</tr>
<tr>
<td><strong>After Imputation Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting CD4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>437.81</td>
<td>230.109</td>
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</tr>
<tr>
<td>Experiment</td>
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<td>410.532</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>507.23</td>
<td>325.532</td>
<td>17</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>446.37</td>
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</tr>
<tr>
<td>Experiment</td>
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<td>360.212</td>
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<td>Total</td>
<td>502.46</td>
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</tr>
</tbody>
</table>

A post hoc power analysis indicated (Keppel, 1991) that 54 participants in each group would have been needed to show the interaction between viral load by group, assuming no participant left the study. (P. Ricci, personal communication, May 28, 2010).

Consequently hypothesis three could not be analyzed. The null hypothesis could be neither accepted nor rejected.

Confounding variables. Two other variables needed to be considered in the context of side-effect symptom control in this study; the first was to account for the use of side effect-reducing medication (SERM). The second confounding variable was how often experimental group participants practiced the CBT techniques taught to them during the intervention visits, progressive muscle relaxation therapy (PMRT), and guided imagery (GI) outside of the
Table 4.12

Descriptive Statistics: Viral Load Means Compared Before and After Imputation

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Imputation Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting VL Absolute Count</td>
<td>Control</td>
<td>74.00</td>
<td>.000</td>
</tr>
<tr>
<td></td>
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<td>36.779</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>81.08</td>
<td>25.038</td>
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<tr>
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<td>Control</td>
<td>128.71</td>
<td>128.239</td>
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<td></td>
<td>Experiment</td>
<td>79.17</td>
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<td>Total</td>
<td>105.85</td>
<td>95.976</td>
</tr>
<tr>
<td><strong>After Imputation Analysis</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Starting VL Absolute Count</td>
<td>Control</td>
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<td>9.221</td>
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<td>180.128</td>
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</table>

<table>
<thead>
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<th>Assignment</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Imputation Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting VL Log_{10}</td>
<td>Control</td>
<td>1.900</td>
<td>.0000</td>
</tr>
<tr>
<td></td>
<td>Experiment</td>
<td>1.933</td>
<td>.1690</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.915</td>
<td>.1104</td>
</tr>
<tr>
<td>Ending VL Log_{10}</td>
<td>Control</td>
<td>1.987</td>
<td>.3364</td>
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<tr>
<td></td>
<td>Experiment</td>
<td>1.898</td>
<td>.1423</td>
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<tr>
<td></td>
<td>Total</td>
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<td>.2591</td>
</tr>
<tr>
<td><strong>After Imputation Analysis</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Starting VL Log_{10}</td>
<td>Control</td>
<td>1.922</td>
<td>.0541</td>
</tr>
<tr>
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<td>.1434</td>
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<td></td>
<td>Total</td>
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<td>.1023</td>
</tr>
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<td>Control</td>
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</tr>
<tr>
<td></td>
<td>Experiment</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.847</td>
<td>.4208</td>
</tr>
</tbody>
</table>

Notes: VL = viral load (serum viral RNA by branched chain DNA assay).
intervention visits. Statistical testing was performed in order to analyze whether or not either of these two confounders affected the results.

The use of SERM was recorded in “checklist” diaries over each of the three months that each participant was in the study. The use of SERM for both groups throughout the study is shown in Figure 4.4. There were no statistically significant differences in SERM use between the groups during the study.

Multivariate testing was used to examine the relationships of each type of SERM (e.g., for nausea) against its effect on the relevant symptom, and whether that affected those differences. The main focus of this testing was on nausea, because there was significantly less nausea reported in the experimental group. Although there was also significant reduction in fatigue in the experimental group, no data were collected on SERM for fatigue, because there is no approved medication for fatigue. Therefore no testing for confounding effects for SERM and fatigue was performed.

**Practice of CBT Techniques.** Multivariate analysis, again, showed no significance for multivariate, within-subject effects, or within-subject contrasts. The data file was split to exclude controls (which did not practice CBT) and bivariate analysis was performed on daily practice against each of the 12 symptom variables. At T3, practice frequency was significantly correlated with symptoms scores for usual nausea, duration of nausea, and usual pain (Table 4.26). No other significant correlations were found. Practice per day of the CBT techniques ranged from none (zero) to approximately nine times per week (1.29); two different participants each were missing data for each of the measurements.
Figure 4.3 SERM Use by Participants During the Study

Note: Bars display means and are grouped by measurement interval. 2 = during participants' first month in the study. 3 = during second month. 4 = from end of second month to study exit.
Table 4.13

Correlations Between Average Daily Practice and VAS Symptom Scores

<table>
<thead>
<tr>
<th></th>
<th>Time 3</th>
<th></th>
<th></th>
<th>Time 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>Sig.</td>
<td>r</td>
<td>Sig.</td>
<td></td>
</tr>
<tr>
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<td>.79*</td>
<td>.03</td>
<td>.18</td>
<td>.66</td>
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</tr>
<tr>
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<tr>
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<td>.35</td>
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<tr>
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<td>.33</td>
<td>.42</td>
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<tr>
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<td>.44</td>
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<tr>
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<td>-.07</td>
<td>.87</td>
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<tr>
<td>Fatigue Usual</td>
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<td>.38</td>
<td>.07</td>
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<tr>
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<td>.24</td>
<td>.57</td>
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<tr>
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<td>.36</td>
<td>.43</td>
<td>-.23</td>
<td>.59</td>
<td></td>
</tr>
</tbody>
</table>

Notes. *, Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed). Positive correlations equate with symptoms increase with frequency of practice. Negative correlations equate with decreasing symptoms with increasing practice. Sig: significant.

Summary of Data Analysis

The sample was analyzed and found to be predominantly composed of white males.

Mean time on ART was 200 weeks. Random assignment did produce otherwise equivalent groups with no significant differences in symptom scores, SF-36 scores, adherence, or clinical measures at study entry.

Hypothesis testing was conducted using Mann-Whitney U. The experimental group reported significantly lower mean symptom scores on nausea and fatigue. In the first case, the null hypothesis asserted that there would be no difference between the experimental and
control groups in symptom scores. The null hypothesis was rejected. The first hypothesis, that participants in the experimental group would have fewer side effects, as evidenced by lower symptom scores, was accepted.

In the second case, the null hypothesis asserted that there would be no difference in adherence between the experimental and control groups at the close of the study. No differences were found and the null was accepted. Mean adherence in both groups throughout the study exceeded 90%.

In the third case, the null hypotheses asserted that there would be no difference between the experimental group and the control group on CD4 and VL. No significant differences were found. The null hypothesis was accepted.

Two confounding variables were tested for their correlation with symptom scores, practice frequency of PMRT and GI, and use of SERM. The mean daily practice frequency was 1.29 times per day. Increasing practice frequency of PMRT and GI was associated with increasing symptom scores for nausea. The mean use of SERM per day for any symptom was <1 dose per day. No correlation of SERM use with symptom scores was found.
Chapter 5

Discussion and Implications

This chapter discusses the results of the study in terms of the hypotheses that were proposed, limitations of the study, and implications of the results for nursing practice. Both the hypothesis testing and recruitment issues are then linked to theoretical discussion in Chapter 1.

Discussion of the Results

Hypothesis One. It was expected that HIV/AIDS patients would experience improvements in subjective symptom complaints related to ART following CBT intervention over time, similar to oncology patients who had received similar CBT interventions in other studies (Loscalzo, 1996; Redd, et al., 2001) The first hypothesis proposed that participants in the experimental group would report lower side effect symptom scores compared to those in the control group. Participants who received the CBT intervention reported significantly less nausea and fatigue than those who did not receive the intervention.

Higher levels of nausea were correlated with increasing frequency of practice of the CBT techniques taught to participants, progressive muscle relaxation therapy (PMRT) and guided imagery (GI) The positive correlation suggests that practice of CBT was associated with increased symptoms at one point during the study. This was an unexpected and paradoxical finding. Negative correlations would be expected if practice lowered symptom scores. No other symptom scores were positively correlated with practice in this way. Such an association is not consistent with the findings in other studies of CBT in anticipatory nausea and vomiting (Burish, et al., 1987; Burish & Jenkins, 1992; Burish & Lyles, 1979; Burish & Lyles, 1981; Burish & Tope, 1992; Carey & Burish, 1987; Carey & Burish, 1988;
Morrow, et al., 1992; Mundy, et al., 2003; Redd, et al., 2001). However Zachariae et al. (2007) note that autonomic sensitivity can make nausea worse when it is part of a conditioned response. This suggests that thinking about nausea may make it worse, for some people. In ART indefinite therapy that is generally less intensely emetogenic is the rule. Indeed, in this study, levels of nausea ranged from about 20 to less than 45 on the VAS for all aspects of nausea that were measured. However, standard deviations ranged from approximately 20-34, which means that nausea was relatively modest in many participants, and was intense, frequent or was of lengthy duration in a only few of the participants. It is thus difficult to link the results of this study to that in oncology, given that in studies of CBT and oncology (Arakawa, 1995, 1997; Burish & Lyles, 1979) there was much more focus on nausea. This would be interesting to study further.

**Hypothesis Two.** It was hypothesized that the CBT intervention could have an effect on adherence to medications over time. The null hypothesis was accepted because no statistically significant differences between the groups were found. The sample results were examined across the duration of the study, as well as between groups.

The adherence VAS and 3-day recall were significantly correlated with each other, and thus reinforced each test’s validity and reliability. What was striking about the results was not that the CBT intervention seemed to have no influence on adherence, but rather that adherence was so high throughout the study. As was discussed in Chapter 2, adherence to the antiretroviral regimen is considered a cornerstone of effective disease management in HIV/AIDS (Press, et al., 2002).

Although adherence is generally high initially, over the course of one to two years it can drop to 67%—only 2/3 of patients are adherent to 95% of doses (Chesney, 2003;
Mannheimer, et al., 2002). Mean duration of ART in the sample of participants in the present CBT trial was about four years. Thus it would be expected that adherence would have averaged what has been reported in those other studies. As was noted in the review, adherence has been shown to be influenced by a variety of factors including depression (Boarts, Sledjeski, Bogart, & Delahanty, 2006), patients’ ideas about their illness and its treatment (Wilson, et al., 2002), active substance abuse (Mellins, Kang, Leu, Havens, & Chesney, 2003; Tanney, Naar-King, Murphy, Parsons, & Janisse, 2010) and other life factors such as stressful events in the home (Mellins, et al.). This study did not collect data on those factors, so the extent of such factors in the sample is unknown. Data on socioeconomic status were also not collected. One explanation for the finding of high reported adherence in both groups throughout the study may be that patients who manage to take ART for longer than two years are more likely to remain adherent. However, this is not replicated when compared with large, longitudinal cohort studies that have shown adherence to decline from >90% to 80% over 4 years (Lazo et al., 2007) and to 51.8% at a mean duration of ART of 4.5 years. There are several possible reasons that the participants in this study reported exceptional adherence: selection bias, poor recollection of actual adherence, deliberate misreporting, lessened drug toxicity with newer agents, or better ways to treat side effects. No significant differences in adherence were found over time, and given the high levels reported in both group, it is unlikely that the sample was large enough to detect any difference.

**Hypothesis Three:** It was hypothesized that the CBT intervention could have an effect on laboratory measures, CD4 counts and VL. There were many missing data points, and both the raw data, and data based on imputed values, were described. The means, variance and standard deviations changed little as a result. However, owing to the wide
variance and large standard deviations both before and after imputation analysis, as well as
the small sample size and low statistical power it was decided that there was insufficient data
from which to draw conclusions. Moreover, recent evidence calls into question the current
clinical approach that utilizes CD4 lymphocyte counts as an “absolute” measure of immune
competence against opportunistic infection. Robustness of viral containment by CD8
lymphocytes, natural killer (NK) activity (Alter & Altfeld, 2009), CD4/CD8 ratio (Forbi &
Agwale, 2009), and expression of CD38 and the immunopathogenic factor programmed cell
death (PD-1) (Holm, Pettersen, & Kvale, 2008) may factor more significantly than CD4
counts alone, which themselves are subject to considerable variation due to factors other than
virus level alone (Amatya et al., 2004).

Limitations of the Study

Sample Size and Composition. While the strength of the study design was that it
tested the intervention against an untreated control group, the sample size was small.
Although the study was fully enrolled (n = 33), only slightly over half of the enrollees
completed the trial. The sample was overwhelmingly male. Females now make up some 26%
of the population with HIV/AIDS (CDC MMWR, 2005), so the sample did not adequately
represent the sex distribution in the general population. The sample was also overwhelmingly
made up of white men. This tends to limit the clinical applicability to similar populations.
However, given the moderate effect size of CBT interventions in other studies and this one,
and the greater likelihood of type II error in smaller samples, the multiple statistically
significant individual comparisons in VAS scores found in favor of the intervention in this
study are remarkable, since multiple effects in favor of the experimental group’s nausea and
fatigue scores was observed despite the actual effect sizes (<1.00) observed in the sample.
Adherence. Interestingly, the participants in both the experimental group and the control group had a very high adherence to ART. With respect to the second hypothesis, any potential impact of CBT on adherence would have been difficult to improve upon simply because of the already very high adherence reported in this study. Clinically significant improvement in adherence was probably not possible, even if the CBT intervention was found to have a statistically significant effect.

Variations in Laboratory Testing and Missing Laboratory Data. Most CD4 counts and viral loads were performed by the same medical center laboratory, but not all were. This introduced a confounding variable in the analysis of that data.

Missing data. Much missing laboratory data led to using an algorithm to generate imputed values for missing CD4 counts and viral loads. Several participants simply did not have their laboratory tests done as requested by their medical providers. No data were collected on why this was the case. The clinical staff suggested that despite their best efforts, such missed testing is commonplace.

Premise of the Study and Issues in Recruitment of Participants

As was noted in Chapter 1, the impetus for this study developed from the clinical experiences of the investigator while working with HIV/AIDS 1996-2002 and involved patients who fared poorly on ART due to intense and intractable side effects. Furthermore, an exhaustive review of the literature showed that little research had been done in attempting to mitigate the side effects of ART in HIV/AIDS patients. This study was conducted to gain further insight into the effects of CBT on adverse symptomatology and thus, fill this gap in the literature. This study is a step toward filling that gap.
The low rate of recruitment was reported in Chapter 4 from data that tracked each participant’s progress through the study. However, no data were collected about why some people chose not to participate. Limited data were collected on why people withdrew. Many patients were potentially eligible for the study, as they were on ART. The clinic database, updated at each patient visit, showed that approximately 90% of those patients eligible to be on ART were prescribed ART (Personal communication, J. Zurlo, March 19, 2007). Little had changed by the time the study commenced in September 2008, and about 90% of the clinic’s population was on ART (Personal communication, D. Greenawalt, September 2, 2008). Those few patients in the infectious disease clinic who were not on medications, fell into two general categories: 1) they were ineligible for treatment based on the guidelines for VL and/or CD4 count (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2009); or, 2) were ineligible for “other reasons,” including active substance abuse (Personal communication, D. Greenawalt, September 2, 2008). Screening by clinic staff eliminated many patients due to 1) lack of reports of side effect symptoms; 2) belief that the person lived “too far away” to participate; or, 3) that the patient “would not be good” for the study. This reduced the pool of patients for consideration of enrollment.

Admission to the study was offered to those patients who the staff had screened for participation as noted above. Patients were not questioned about why they chose not to participate, as this could be interpreted as coercion. One of the hallmarks of ethical research is non-coercion (Polit & Beck, 2004), and the investigator wished to avoid putting patients “on the spot” when they are already in the vulnerable position of having HIV/AIDS. However, some patients volunteered their reasons for non-participation:

- “I have too much going on right now.”
• “I have transportation issues.”

• “I don’t think my problems are from the medicine.” (From personal communications kept in author’s notes and not specifically attributed for anonymity, September 9, 2008 through June 10, 2009.)

Scheduling with the psychologist for the intervention was a major concern expressed with respect to the first two reasons stated. For those participants who were scheduled and completed the series of three visits with the psychologist expressed very positive statements about the experience and the techniques they learned. Nevertheless, scheduling not only appeared to interfere with keeping medical appointments (Personal communication, D. Greenawalt, April 28, 2009), but appeared to have some bearing on whether patients felt they had the time to be in the study.

The third statement concerning patients who felt their symptoms were not medication related was discussed earlier. It was assumed that patients know the difference. However it is possible that they did not always know what momentary complaints were related to: HIV, co-morbidities, or side effects. In summary, in addition to the restrictive selection by the clinic staff, low recruitment may be related to patients’ concern about scheduling and availability for the intervention, as well as lower reported side effect symptoms than expected.

Theoretical Framework

The theoretical framework for this study was based on cognitive control of autonomic responses which would lead to lessening of autonomic symptoms caused by patients’ experience with ART. In the first chapter, anxiety was discussed as being both a symptom and an amplifier of the discomfort associated with other symptoms such as nausea/vomiting, pain, and fatigue. The literature review discussed the success seen in reducing symptoms
associated with antineoplastic therapy in cancer treatment. It was reasonable to theorize that such CBT-related symptom reductions would apply in ART as well. In this study the significant effects of the CBT intervention on side effects symptoms are consistent with previous research, although the sample composition suggests limits to generalization to all HIV/AIDS patients on ART.

In this study, anxiety and pain were not significantly different between the groups. As noted in Chapter One anxiety is itself a symptom, and it has been theorized that anxiety also amplifies other symptoms, such as pain (Adams & Field, 2001; Adams, et al., 2006; Colloca & Benedetti, 2007), nausea (Burish & Carey, 1986), and fatigue (McCann & Boore, 2000). It was expected that the findings of any decreased symptom—and in this study nausea and fatigue were decreased in the experimental group—would co-occur with findings of decreased anxiety, but this was not observed. It is possible that small sample size led to an inability to detect changes in anxiety. It is also possible that anxiety has variable effects on other side effect symptoms, and that CBT may modify such symptoms without also modifying anxiety, especially in participants whose anxiety was low and other symptoms were high. The sample size was not large enough to detect such interactive effects. The experimental group failed to benefit with reduced anxiety from the CBT intervention, and this runs contrary to both the literature and the theory (Hunot, Churchill, Silva de Lima, & Teixeira, 2007). They did, however, benefit from the intervention with respect to nausea and fatigue which is concordant with the literature on CBT in oncology (Carey & Burish, 1988; Morley, et al., 1999; Mundy, et al., 2003; Redd, et al., 2001).
Suggestions for Further Research

The results of this study suggest that CBT can help highly medication-adherent, male HIV/AIDS patients on ART experience less nausea and fatigue, after only three CBT sessions that include progressive muscle relaxation therapy (PMRT) and guided imagery (GI), techniques that can be practiced outside the clinic, as patients feel the need to do so. It was noted in Chapter Two that to date, no study had been published that tested individualized, brief-contact CBT as a means of reducing side effect symptoms from ART. Studies of CBT in symptom management have tended to employ a larger number of therapeutic encounters. This is the only study that employed such a small number of therapeutic encounters. The results of this study suggest that further exploration of brief-contact CBT-type interventions for symptom reduction should be explored further.

A larger study could be employed to examine the effects of CBT on symptom reduction in women as well as men, in patients who are less adherent to ART, and in a wider array of socio-cultural/ethnic groups. Further, a larger study enrolling more participants might detect similar positive effects with respect to pain and anxiety. It would be useful to expand the planned analysis of a larger sample to explore how individual practice of CBT techniques influences symptom intensity, frequency, and duration, since there was positive correlation between CBT practice and nausea. Although significant, this correlation may have been by chance, and a larger study, designed to better detect such relationships, could provide further clarity.

The recruitment and dropout rates, as well as anecdotal reports from candidates for and participants in this study suggest that designing a larger study to recruit patients living with HIV/AIDS to further study the effects of CBT on symptoms might not be practical
without expanding enrollment to include multiple sites. Despite having access to some 600+ patients, only 18 completed the study. Although it is possible enlarging the pool of potential participants in a multi-center trial would improve sample size, it was also true that clinic staff controlled who was enrolled. Antiretroviral therapy to treat HIV disease has been in continuous development since the 1980s, and following the success of multi-class antiviral therapy in the mid-1990s, regimens have been improved with corresponding decreases in side effects (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2009). Since this is the case, fewer patients may benefit from CBT employed for the purpose of reducing side effect symptoms. It is also possible that such symptoms are more burdensome early in ART, and this study was not designed to select for those individuals. A follow up study might target only patients on a new regimen.

Implications for Nursing Practice

The findings of this study lend support to the idea that a brief series of CBT sessions can help to reduce symptom discomfort, at least for nausea and fatigue in HIV/AIDS patients taking ART. In this sample, medication therapy is of life long duration. In long term ART, symptoms can continue indefinitely as well. Nevertheless and despite a limited array of change, significant changes were observed in the small sample used in this study. Moreover, the intervention itself displayed no evidence of harm. In general CBT carries a low risk of adverse effects when the sessions are focused on reducing autonomic arousal and inducing relaxation for beneficial effects (J. S. Beck, 1995). Thus, given even the modest findings in this study and the relative safety of CBT as practiced in this study, it is reasonable for nurses to consider CBT interventions for HIV/AIDS patients who suffer from nausea and/or fatigue.
as while on ART. The brevity of the contact with CBT in this study creates a framework for in-clinic trainings by nurses familiar with CBT methods like those used in this study.

Conclusions

In this study CBT was delivered in a small dose of three visits by a behavioral interventionist to HIV/AIDS patients with any of four functional symptoms associated with ART including fatigue, pain, nausea and anxiety. In this small clinical trial, the experimental group reported significantly lower scores, compared to the control group, over time for some measures of fatigue and nausea, but not pain or anxiety. The study was limited by low enrollment, in part due to the lack of symptoms reported by patients as newer ART drugs have been developed and marketed. A high dropout rate occurred and may have been due to several causes including the difficulty of scheduling time with the behavioral interventionist, as well as medical visits, which were separate from the study visits. Even with this small sample, the study’s results suggest that CBT has some benefit for treating fatigue, and nausea in these patients. Cognitive-behavioral therapy, as the study intervention, had no effect on the biological parameters of CD4, viral load, or adherence to therapy. However adherence for this study sample was reported overall to be higher than has been reported in HIV/AIDS literature. Interestingly, in this study CD4 and VL were not correlated, nor was adherence correlated with CD4 or VL. Moreover, the majority of participants had VLs that were “undetectable” with values below the cutoff of 75 copies of viral RNA per mL. Little else could be done to improve upon adherence and virus levels in this sample. There may have been unintentional bias in how clinic staff prescreened patients for enrollment, and may have represented the bias of the clinic providers who identifying individuals who they “thought” would be appropriate for the study. The results of this study provide more insight into the
management of the symptoms associated with ART in HIV patients, and suggest that CBT may be a useful clinical tool to help reduce side effects of ART, at least in some patients.

The results suggest that a larger study might be worthwhile. A follow up trial might focus on those patients most likely to have symptoms, patients who begin new regimens. The effects of individual practice of the CBT techniques used in this study by patients (having been taught those techniques by a therapist) might be studied, since individual practice was unexpectedly correlated with increasing nausea. The effects seen from the small dose of CBT and the problems encountered with recruiting and scheduling for the separate intervention suggest that bringing such an intervention into the clinic and parallel with medical treatment could prove valuable. This could easily be incorporated into nursing practice. Non-drug interventions that fit into care models of nursing and skill set offer an important avenue to reducing patient symptoms and improving their quality of life. The findings from this study offer evidence that simple CBT techniques are useful for achieving improvements in patient comfort, and can serve as a starting point for a promising line of research.
References


Bangsberg, D. R. (2006). Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clinical Infectious Diseases, 43*(7), 939-941.


### APPENDIX A

**DEMOGRAPHIC DATA FORM**

<table>
<thead>
<tr>
<th>Medication Side Effect Study Demographic Data Form</th>
<th>PARTICIPANT NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initials – Birthdate – 2-digit sequence number</td>
</tr>
<tr>
<td></td>
<td>DATA COLLECTOR</td>
</tr>
<tr>
<td></td>
<td>DATE</td>
</tr>
</tbody>
</table>

Instructions: circle or complete each item as it applies

1. **Biologic sex**
   - male [1]
   - female [2]
   - endocrine transsexual process, M→F [3]
   - endocrine transsexual process, F→M [4]
   - surgical transsexual process, M→F [5]
   - surgical transsexual process, F→M [6]

2. **Racial/ethnic group**
   - Caucasian [1]
   - Caucasian Hispanic [2]
   - African American [3]
   - African [4]
   - African Hispanic [5]
   - Other Hispanic [6]
   - East Asian [7]
   - South Asian [8]
   - Pacific Islander [9]

3. **Understand/read/speak English?**
   - yes [1]
   - no [2]

4. **Age (number):** _____________

5. **Duration of ART weeks:** _____________

6. **Does candidate suffer from any of the following that are related to ART?**
   - Nausea &/or vomiting [1]
   - Fatigue [3]
   - Pain [2]
   - Anxiety [4]
APPENDIX B

MEASUREMENT INSTRUMENTS

Facsimiles of the instruments appear on the following pages.
INSTRUCTIONS

We would like to know how you feel about a few ordinary things today. There are several things listed on the following pages. Each thing is a symptom or a feeling you may experience while on HIV medication. Each question asks you about how strong the feeling or symptom is, or how long you have been experiencing it. With each question there is a line that looks like this:

MOST

The LEAST or NONE

The bottom of the line is the lowest, or least amount. The top is the most, strongest, or worst feeling.
And each line will have words that describe your feelings about the thing, a rough number of the thing (like a few or many), or how long it lasts. Like this example:

**FOOD: how tasty was your last meal?**

For each item, use the red pen to make a mark on the line that most describes the LEVEL of the thing or how long it lasts. Like this:

That’s all there is to it! Please turn to the next page and complete the items. If you have any questions, feel free to ask the research associate for help.
These three questions are about NAUSEA, “sickness in the stomach,” or “queasiness”

1. Mark the line with the **usual** amount of nausea in the last month

2. Mark the line with the **worst** amount of nausea in the last month

3. Mark the line with the **length of time** you typically felt nausea in the last month
These three questions are about PAIN of any sort

1. Mark the line with the **usual** amount of pain in the last month

   The worst ever

   None

2. Mark the line with the **worst** amount of pain in the last month

   The worst ever

   None

3. Mark the line with the **length of time** you typically felt pain in the last month

   All the time

   None

Next Page
These three questions are about ANXIETY, “nervousness,” or “worry”

1. Mark the line with the **usual** amount of anxiety in the last month
2. Mark the line with the **worst** amount of anxiety in the last month
3. Mark the line with the **length of time** you typically felt anxiety in the last month

<table>
<thead>
<tr>
<th>PARTICIPANT NUMBER</th>
<th>DATE OF COMPLETION</th>
<th>MEASUREMENT NUMBER</th>
<th>DATA COLLECTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The worst ever

None

The worst ever

None

All the time

None
These three questions are about FATIGUE, “tiredness,” or “no energy”

1. Mark the line with the **usual** amount of fatigue in the last month
   The worst ever

2. Mark the line with the **worst** amount of fatigue in the last month
   The worst ever

3. Mark the line with the **length of time** you typically felt fatigue in the last month
   All the time

None

None

None

Go onto the next page
These questions are about taking your HIV medications

Mark the line with the number of doses of prescribed HIV medication you took in the last month:

100%  90%  80%  70%  60%  50%  40%  30%  20%  10%  None

In the last 3 days, how many doses of medication were you scheduled to take?

How many did you actually take?
Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an \( \blacksquare \) in the one box that best describes your answer.

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

   \[
   \begin{array}{cccccc}
   \text{Excellent} & \text{Very good} & \text{Good} & \text{Fair} & \text{Poor} \\
   \blacksquare & \blacksquare & \blacksquare & \blacksquare & \blacksquare
   \end{array}
   \]

2. Compared to one year ago, how would you rate your health in general now?

   \[
   \begin{array}{ccccc}
   \text{Much better now than one year ago} & \text{Somewhat better now than one year ago} & \text{About the same as one year ago} & \text{Somewhat worse now than one year ago} & \text{Much worse now than one year ago} \\
   \blacksquare & \blacksquare & \blacksquare & \blacksquare & \blacksquare
   \end{array}
   \]
3. 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?

<table>
<thead>
<tr>
<th>Activity Description</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Climb several flights of stairs</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Climb one flight of stairs</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Bending, kneeling, or stooping</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Walking several hundred yards</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Walking one hundred yards</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
<tr>
<td>Bathing or dressing yourself</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
</tbody>
</table>
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
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</tr>
</tbody>
</table>

- Cut down on the amount of time you spent on work or other activities
- Accomplished less than you would like
- Were limited in the kind of work or other activities
- Had difficulty performing the work or other activities (for example, it took extra effort)

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Cut down on the amount of time you spent on work or other activities
- Accomplished less than you would like
- Did work or other activities less carefully than usual
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very Mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did you feel full of life?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>2. Have you been very nervous?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>3. Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>4. Have you felt calm and peaceful?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>5. Did you have a lot of energy?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>6. Have you felt downhearted and depressed?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>7. Did you feel worn out?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>8. Have you been happy?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>9. Did you feel tired?</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

SF-36® Health Survey © 1994, 2000 by QualityMetric Inc. and Medical Outcomes Trust. All Rights Reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
SF-36 v2.0 (1/08/2001)
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th></th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don't know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>I seem to get sick a little easier than other people</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am as healthy as anybody I know</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I expect my health to get worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My health is excellent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

THANK YOU FOR COMPLETING THESE QUESTIONS!
INSTRUCTIONS

Your packet contains a calendar and the research associate has marked the calendar with your study starting date. During the study, each time you practice the methods in your personalized recording, mark that on the day that you did so. For example if you practiced once on Thursday, March 20\textsuperscript{th}, Saturday March 22\textsuperscript{nd}, and Wednesday, March 26\textsuperscript{th} then you would mark the calendar like this:

<table>
<thead>
<tr>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>21</td>
<td>22</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>\textit{Practice}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>\textit{Practice}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

That’s all there is to it! You may practice your recorded exercises as often as you feel it is necessary to maintain your health. If you have any questions, contact a research associate at (717) 948-6513.
APPENDIX C

RECORDING SHEETS FOR THE USE OF SERM

Facsimiles of this instrument appear on the following pages.
INSTRUCTIONS

This is a diary to help you let us know how many doses of medicine you have used to reduce side effects. Just fill in the date you took the medicine. Go from top to bottom in each column, and when you run out of space, start at the top of the next column. If you take more than 1 dose on a given day, you can just make a checkmark below that date. *Like this:*

<table>
<thead>
<tr>
<th>Medicines for NAUSEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/3/07</td>
</tr>
<tr>
<td>□</td>
</tr>
<tr>
<td>□</td>
</tr>
<tr>
<td>□ 3/11/07</td>
</tr>
<tr>
<td>3/4/07</td>
</tr>
<tr>
<td>□</td>
</tr>
<tr>
<td>□ 3/5/07</td>
</tr>
<tr>
<td>3/7/07</td>
</tr>
<tr>
<td>□</td>
</tr>
<tr>
<td>□ 3/9/07</td>
</tr>
<tr>
<td>3/10/07</td>
</tr>
</tbody>
</table>

There is a diary chart for each type of side effect medicine we need to know about.

Just write in the date when you take your first dose that day.

Then just make a check mark if you take any more doses that day.

If you run out of room, we have included a blank diary for you to fill in as needed.
<table>
<thead>
<tr>
<th>DIARY DATES</th>
<th>FROM</th>
<th>TO</th>
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</table>

**Medicines For PAIN**

<p>| | | |</p>
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</table>

**Medicines For NAUSEA, “sickness in the stomach” or queasiness**

<p>| | | |</p>
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</tbody>
</table>
Medicines For ANXIETY or nervousness

<table>
<thead>
<tr>
<th>Protocol # 000-0000-XXX : PARTICIPANT NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIARY DATES</td>
</tr>
<tr>
<td>DATA COLLECTOR NUMBER</td>
</tr>
</tbody>
</table>

If you need more pages, please contact a research associate. Thank you!
APPENDIX D

INFORMED CONSENT

A facsimile of this document appears on the following pages.
CONSENT FOR RESEARCH
Penn State College of Medicine
The Milton S. Hershey Medical Center

Title of Project: Pilot Study of Cognitive-Behavioral Therapy to Reduce Antiretroviral Side Effects in HIV Patients

Principal Investigator: Robert Eric Doerfler, CRNP, PhDc

Other Investigators: Kathrine Bakke-Friedland

Participant's Printed Name: __________________________

This is a research study. Research studies include only people who want to take part. This form gives you information about this research, which will be discussed with you. It may contain words or procedures that you don’t understand. Please ask questions about anything that is unclear to you. Discuss it with your family and friends and take your time to make your decision.

1. **Purpose of the Research:**
   You are being offered the opportunity to take part in this research because you are receiving HIV medications and experiencing side effects from these medications. The purpose of this research is to study whether or not certain psychological therapy techniques can reduce the side effects that commonly happen when a person is on HIV medications.

   Approximately 30 people will take part in this research at the Hershey Medical Center.

2. **Procedures to be Followed:**
   If you agree to take part in this research you will be asked to sign this consent form. We will review your medical records for information about your HIV medications, your CD4 count and HIV levels. We will ask you questions about any side effects you are experiencing from your HIV medications.

   If you qualify for the research based on this information:
   - You will be asked to complete several surveys about the side effects you are experiencing, about your quality of life and about taking your HIV medications. You will complete these surveys four times: when you start the research and after 30, 60 and 90 days.
You will be asked to keep a diary of the number of doses of medications taken to reduce the side effects from your HIV medications. This information will be reviewed when you qualify for the research and after 30, 60 and 90 days.

Information from your medical record (including your CD4 counts and HIV levels) will be recorded for this research when you start the research and at the end of the study.

You will be randomly assigned (assigned by chance, like flipping a coin) to one of two groups. You will have an equal chance of being assigned to either one of the two groups.

- Group one - Usual care group – This group receives the usual education about the medications and their side effects. OR
- Group two – Intervention group – This group receives the usual education about the medications and their side effects plus three (3) sessions with a licensed therapist who will show you psychological therapy techniques to help you deal with side effects from HIV medications.

If you are assigned to the usual-care group, you will be given two packets of surveys and diaries to complete: one at 30 days and the other at 60 days. They will be dated so you know when to complete them. After you complete them you can return them in the mail. At the end of the study (90 days) you will be asked to return to the clinic for your last study visit. At this visit we will help you complete the final surveys.

If you are assigned to the intervention group, you will have three sessions with a psychologist at School of Nursing facility in the Academic Support Building at the Medical Center. The therapist will teach you how to tense and relax your muscles and gently control your breathing in order to reduce anxiety. The therapist may also help you think of pleasant associations and images in order to help relaxation. You will be given the chance to record a tape, CD or MP3 file for use in the audio device of your choice, so you can practice on your own. If you need an audio device, one will be provided for you at no cost. You will be asked to complete a calendar that records the number of practice sessions you perform on your own. Your 30- and 60-day surveys will be completed at the second and third therapy visits. You will be asked to return to the clinic for your last study visit at 90 days. At this visit we will help you complete the final surveys.

No matter which group you are assigned to, you will continue to receive your regular medical care with your usual health care provider. You may ask your health care provider as many questions as you want about how to take your medicines properly.

3. Discomforts and Risks:
The therapy sessions may make you uncomfortable or distressed. If this happens we will help your medical provider refer you to psychological services.
There is a risk of loss of confidentiality if your medical information or your identity are obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

4. Possible Benefits:
   a. Possible benefits to the participant:
      If you are assigned to the usual care group you will not benefit from taking part in this research. If you are assigned to the intervention group, you may have more effective control of bothersome side effects from your HIV medications. There is no guarantee that you will benefit from being in this research.

   b. Possible benefits to others:
      Information from this study may help us learn if psychological therapies can help people deal better with their HIV medications.

5. Other Options that Could be Used Instead of this Research:
   You do not have to take part in this research study. You may receive the usual education about the medications and their side effects without being in this research study.

   Because they are experimental in HIV patients, the psychological therapy techniques offered in this research are only available to you if you take part in the research study.

6. Time Duration of the Procedures and Study:
   If you agree to take part in this study, your involvement will last approximately 3 months. You will be asked to return to the clinic 4 times if you are in the intervention group, and only two times if you are in the usual care group. Each clinic visit will take approximately an hour and 20 minutes if you are in the intervention group, and only 30 minutes if you are in the usual care group.

7. Statement of Confidentiality:
   a. Privacy and confidentiality measures
      Your records that are used in the research at The Milton S. Hershey Medical Center (HMC) and Penn State (PSU) will include a code number, your name, address, phone number, date of birth, and medical record number. These records will be kept in a secured area in principal investigator's office.

      For research records sent to investigators in this study at Duquesne University, you will be identified by a code number. The list that matches your name with the code number will be kept in a locked file in the principal investigator's PSU office.

      In the event of any publication or presentation resulting from this research, no personally identifiable information will be shared.

   7b. The use of private health information:
      If you give your consent, health information about you will be collected for this research. Health information is protected by law as explained in the HMC Privacy Notice. If you have not received this notice, please request a copy from the researcher.
At HMC/PSU your information will only be used or shared as explained in this consent form or when required by law. However, some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information and may share it without your permission.

If you do not want us to use your protected health information, you may not participate in this research. The research-related therapy is investigational; therefore, it is not available unless you allow the use of your health information that is collected during this research study.

Your permission for the use, storage, and sharing of your identifiable health information will end when the research study is completed. At that time the research information will be destroyed. Any research information in your medical record will be kept indefinitely.

If you choose to participate, you are free to withdraw your permission for the use and sharing of your health information at any time. You must do this in writing. Write to R. Eric Doerfler, CRNP and let him know that you are withdrawing from the research study. His mailing address is Olmsted W 331, 777 West Middletown Pike, Middletown, PA 17057.

If you withdraw your permission:
- We will no longer use or share medical information about you for this research study, except when the law allows us to do so.
- We are unable to take back anything we have already done or any information we have already shared with your permission.
- We may continue using and sharing the information obtained prior to your withdrawal if it is necessary for the soundness of the overall research.
- We will keep our records of the care that we provided to you as long as the law requires.

The research team may use the following sources of health information:
- Information from your medical record related to this research study
- Information from your completed questionnaires and diaries

Representatives of the following people/groups within HMC/PSU may use your health information and share it with other specific groups in connection with this research study.
- The principal investigator, R. Eric Doerfler, CRNP
- The HMC/PSU Institutional Review Board
- The HMC/PSU Human Subjects Protection Office
- The research team

The above people/groups may share your health information with the following people/groups outside HMC/PSU for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original PSU/HMC records.
8. **Costs for Participation:**
   There is no cost to you for participating in this study. If you are assigned to the intervention group, neither you nor your insurance will be charged for the therapy sessions that are part of this research study. You will not lose any legal rights by signing this form.

9. **Compensation for Participation:**
   If you are in the usual-care group, you will receive $10 (ten dollars) for each survey completed. If you are in the experimental group, you will receive $10 (ten dollars) for each survey and therapy session you complete. This compensation is for your time and any inconvenience associated with the study.

10. **Research Funding:**
    The investigators are receiving a grant from PSU to support this research.

11. **Voluntary Participation:**
    Taking part in this research study is voluntary. If you choose to take part in this research, your major responsibilities will include completing the surveys and attending the therapy sessions if you are assigned to the intervention group. You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which you are entitled.

12. **Contact Information for Questions or Concerns:**
    You have the right to ask any questions you may have about this research. If you have questions, complaints or concerns or believe you may have developed an injury related to this research, contact the Principal Investigator, Eric Doerfler, at 717-948-6513.

    If you have questions regarding your rights as a research participant or you have concerns or general questions about the research or about your privacy and the use of your personal health information, contact the research protection advocate in the HMC Human Subjects Protection Office at 717-531-6887. You may also call this number if you cannot reach the research team or wish to talk to someone else.

    For more information about participation in a research study and about the Institutional Review Board (IRB), a group of people who review the research to protect your rights, please visit the HMC IRB’s Web site at [http://www.hmc.psu.edu/irb](http://www.hmc.psu.edu/irb). Included on this web site, under the heading "Participant Info", you can access federal regulations and information about the protection of human research participants. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-6887.
Signature and Consent/Permission to be in the Research
Before making the decision regarding enrollment in this research you should have:
- Discussed this study with an investigator,
- Reviewed the information in this form, and
- Had the opportunity to ask any questions you may have.
Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Participant: By signing this consent form, you indicate that you are voluntarily choosing to take part in this research.

Signature of Participant __________________________ Date __________ Time ______ Printed Name ______

Person Explaining the Research: Your signature below means that you have explained the research to the participant/participant representative and have answered any questions he/she has about the research.

Signature of person who explained this research __________________________ Date __________ Time ______ Printed Name ______
(Only approved investigators for this research may explain the research and obtain informed consent.)
CONFIDENTIALITY AGREEMENT

DUQUESNE UNIVERSITY
600 FORBES AVENUE ♦ PITTSBURGH, PA 15282

CONFIDENTIALITY AGREEMENT FOR: Clinical Trial of Cognitive-Behavioral Therapy to Reduce Antiretroviral Side Effects in HIV Patients, Primary Investigator, R. Eric Doerfler, CRNP, PhD(c)

<table>
<thead>
<tr>
<th>Name of Team Member</th>
<th>Role</th>
</tr>
</thead>
</table>

By signing below I acknowledge that I will be working as a research team member, and that representing such, I will have access to sensitive medical/health information about participants in this study. Some of this information relates to the HIV status and mental health status of research study participants. I understand that all health information is protected by the U.S. Health Insurance Portability and Accountability Act of 1996 and applicable laws of the Commonwealth of Pennsylvania concerning HIV status, mental health, and substance abuse.

I agree to maintain the confidentiality of records and to adhere to the protocols for the security of paper and electronic data, included in the study proposal approved by the Duquesne University Institutional Review Board and the Office of Research.

If I identify a health concern of or hazard for a participant I understand that I am to disclose my concern to the primary investigator and the participant’s treating clinician and/or nurse.

This agreement remains in force after the conclusion of the study and will be kept on file with the primary investigator in accordance with applicable privacy laws and regulations.

____________________________________   _____________________________
Signature of Team Member               Date

____________________________________   _____________________________
Witness                                Date