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The Effects of a Structured Adherence Intervention to HAART on Adherence and Treatment Response Outcomes

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by

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List of Acronyms

AACTG	Adult AIDS Clinical Trial Group
ADAP	AIDS Drug Assistance Program
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
AZT	Zidovudine
CAS	Composite Adherence Score
CASI	Computer-Assisted Self-Interview
CPCRA	Community Programs for Clinical Research on AIDS
DHHS	Department of Health and Human Services
DOT	Directly Observed Therapy
EDM	Electronic Data Monitoring
EI	Entry Inhibitor
HAART	Highly Active Antiretroviral Therapy
HCA	Health Center Administrator
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
MEMS	Medication Event Monitoring System
MSM	Men Who Have Sex with Men
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NP	Nurse Practitioner
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PCP	Primary Care Provider

PI	Protease Inhibitor
PMS	Pharmacy Management System
RCT	Randomized Controlled Trials
RNA	Ribonucleic Acid
SAI	Structured Adherence Intervention
SMAQ	Simplified Medication Adherence Questionnaire
SPSS	Statistical Package for the Social Sciences
TDM	Therapeutic Drug Monitoring
VAS	Visual Analogue Scale

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ABSTRACT

Background: Adherence to antiretroviral (ARV) medications in excess of 90-95% is necessary for optimal response to suppress HIV replication and to maintain and/or restore immune function. A number of interventions have been shown to improve ARV adherence, but no research has been conducted which evaluates proactive monitoring of pharmacy refill adherence and subsequent intervention when inadequate adherence is identified.

Purpose: The purpose of this project was to compare treatment response, pharmacy refill adherence and self-reported medication adherence between two groups of patients: those participating in an AIDS Drug Assistance Program (ADAP) and those participating in a Medicaid-funded medication access program. The ADAP served as a structured adherence intervention (SAI) based on procedural and administrative processes required by the state-managed program. Additionally, covariates that can impact adherence were studied including utilization of adherence services and interventions and factors related to HIV disease, antiretroviral agents and sociodemographic factors.

Method: This retrospective comparative study examined secondary data to assess 424 patients who received clinical and pharmacy services at one treatment site in 2005.

Analysis: Logistic regression was performed to test the effects of the SAI on treatment response (CD4 and HIV RNA response), self-reported adherence, and pharmacy refill adherence while controlling for the covariates.

Results: Patients participating in the SAI demonstrated higher levels of both self-reported and pharmacy refill adherence compared to patients receiving usual care. Although patients participating in the SAI program demonstrated better virologic (HIV RNA) responses to HAART compared to patients receiving usual care, immunologic (CD4 lymphocyte) responses to HAART were not significantly different compared to subjects in the usual care program.

Conclusion/Discussion: This study provides information on the effects of a structured programmatic intervention on medication adherence and response to treatment and will be used to inform policy decision making at the local and State level.

CHAPTER ONE: INTRODUCTION

Background

Human immunodeficiency virus (HIV) infection was originally considered a terminal illness when identified in the early 1980s. Nearly everyone who contracted the disease advanced to Acquired Immunodeficiency Syndrome (AIDS) and death (Bartlett & Gallant, 2005). Treatment with the first antiretroviral agent zidovudine (AZT), which became available in the late 1980s, gave short-term encouragement to those with HIV disease. Within a year, however, most persons no longer responded to this medication and became ill or died. A breakthrough occurred in 1996 with the introduction of an effective combination therapy capable of suppressing HIV replication. These potent combination drug regimens now known as highly active antiretroviral therapy (HAART) redefined HIV disease into a chronic illness requiring long-term management rather than a terminal disease (Johnson et al., 2006). During the last decade, advances in the scientific understanding of HIV dynamics and pathogenesis, the development and widespread use of quantitative HIV ribonucleic acid (RNA) assays to quantify serum levels of HIV, and the availability and use of powerful antiretroviral agents culminated in dramatic changes in HIV clinical care and improved clinical outcomes (Williams et al., 2006).

Adherence

The World Health Organization (2003) broadly defined adherence as the extent to which a patient's behavior, such as taking prescribed medications or following a diet, corresponds with the interventions of the healthcare provider. Medication adherence in HIV disease has been defined as the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a combination medication regimen to control viral replication and improve immune function (Jani, 2002). The terms adherence and nonadherence are meant to be nonjudgmental, statements of fact rather than expressions of blame toward the patient or provider (Bangsberg, Perry et al., 2001).

Highly Active Antiretroviral Therapy (HAART)

Antiretroviral (ARV) drugs for the treatment of HIV disease are broadly classified by the phase of the HIV lifecycle that the drug inhibits. Antiretroviral drugs currently licensed for clinical use by the Food and Drug Administration are classified as nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and entry inhibitors (EI). Table 1 lists these agents by classification and mechanism of action.

HAART is the combination of at least three ARV drugs that target at least two different parts of the HIV lifecycle or stop the virus from entering CD4 lymphocytes. A panel of experts convened by the Department of Health and Human Services regularly publishes guidelines suggesting preferred and alternative combinations that can be combined to form a HAART regimen. HAART typically includes two NRTIs paired with an NNRTI or a PI. In advanced stages of HIV disease or when significant

medication resistance is present, HAART regimens may include more than four or five agents (National Institutes of Health, 2006).

Table 1

FDA Approved Antiretroviral Agents

Classification	Mechanism of Action	Agents
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)	The reverse transcription process is blocked. HIV RNA cannot be converted to HIV DNA and viral reproduction is terminated.	Zidovudine Lamivudine Stavudine Entricitabine Didanosine Tenofovir Abacavir
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	The reverse transcription process is blocked. HIV RNA cannot be converted to HIV DNA and viral reproduction is terminated.	Nevirapine Efavirenz Delavirdine
Protease inhibitors (PI)	Final viral assembly is inhibited when protease enzymes are not available to reassemble viral particles and produce new virus.	Saquinavir Ritonavir Nelfinavir Indinavir Lopinavir/ritonavir Atazanavir Fosamprenavir Tipranavir Darunavir
Entry Inhibitors	The process of HIV binding to a CD4 lymphocyte is interrupted, thus blocking the ability of HIV to infect a CD4 lymphocyte.	Enfuvirtide Maraviroc

Effects of HAART on Outcomes

The introduction of HAART has dramatically decreased morbidity and mortality among HIV-infected patients throughout the developed world (Egger et al., 1997; Hogg et al., 1998; Palella et al., 1998). In the United States, mortality from HIV infection decreased by 70% between 1996 and 1998 and decreased an additional 14% between 1998 and 2002 (Centers for Disease Control, 2004; Frick, Tapia, Grant, Novotny, &

Kerzee, 2006; Hogg et al., 1998; Palella et al., 1998). The incidence of opportunistic infections associated with AIDS has also decreased significantly with the use of HAART (Grabar et al., 2000).

Patients' ability to adhere to complex regimens is an essential component of successful antiretroviral therapy (Kitahata et al., 2004) and is widely regarded as the most important mutable determinant of clinical outcomes in the HIV-infected patient (Wood et al., 2003). Although a decrease in the number of CD4 lymphocytes is the strongest predictor of progression to AIDS and death, adherence to HAART is the second most common predictor (Bangsberg, Perry et al., 2001; Garcia de Olalla et al., 2002; Hogg et al., 2002; Machtinger & Bangsberg, 2006; Wood et al., 2004). In studying levels of adherence, Bangsberg and his team (2001) found that no patients in a group of highly adherent patients developed AIDS-defining events over the 16 months of the study compared to those with moderate and low adherence. Each 10% difference in mean adherence was found to be associated with a 28% reduction in risk of progression to AIDS. Another group concluded that adherence behavior is a dynamic process and continued adherence was associated with improved response to ARV therapy (Carrieri et al., 2001). It has been estimated that a nonadherent patient receiving HAART is 3.87 times more likely to die than an adherent patient on the same therapy (Garcia de Olalla et al., 2002).

Although adherence to HAART at a level above 95% has been associated with optimal viral suppression, the relationship between various levels of adherence, resulting virologic treatment responses, and long-term clinical outcomes has not been determined. Previous studies have examined relatively small numbers of patients in relation to short-

term virologic response to HAART. Adherence to antiretroviral therapy in both the short-term and the long-term is crucial for treatment success and must be continually reinforced (Hammer et al., 2006).

Difficulty Adhering to HAART / Nonadherence

Overview and Implications

The Department of Health and Human Services (DHHS) develops and publishes HIV treatment guidelines on a regular basis. These guidelines reinforce that one of the most important issues in managing patients receiving HAART is adherence to therapy (National Institutes of Health, 2006). When treating HIV disease, adherence levels need to be at the 90-95% level to achieve and maintain therapeutic effectiveness (Murphy, Lu, Martin, Hoffman, & Marelich, 2002; Paterson et al., 2000). Maintaining this threshold can be complex and difficult. Adherence to HAART has been described as the "Achilles'Heel" of antiretroviral therapy (Simoni, Frick, Pantalone, & Turner, 2003) because of the difficulty associated with maintaining such high levels of medication adherence.

There are a number of contributing factors that make 100% adherence to HAART difficult for many patients including the complexity of the HAART regimen (multiple pills, multiple doses, food requirements and restrictions), immediate and long-term side effects associated with the ARV agents, and comorbid conditions such as active substance abuse and mental illness.

Prevalence of Nonadherence

Nonadherence to medication therapy has been a problem for as long as remedies for health conditions have been prescribed (Chesney, 2006). Evidence shows that poor adherence to ARV regimens has serious consequences for HIV-infected patients including failure to prevent viral replication, an increased likelihood of developing viral resistance, decreasing CD4 lymphocyte counts, ineffective disease treatment, increasing illness, advancement to AIDS, and ultimately death (Bangsberg, Hecht et al., 2001; Gifford et al., 2000; Miller & Hays, 2000a; Murphy, Lu, Martin, Hoffman, & Marelich, 2002; Turner, 2002). Despite these risks, nonadherence to HAART is widespread in the United States and in Europe with estimates of the percentage of prescribed doses taken ranging from 60% to 70% (Bangsberg et al., 2000; Bartlett, 2002; Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Martin-Fernandez, Escobar-Rodriguez, Campo-Angora, & Rubio-Garcia, 2001; Moatti et al., 2000; Nieuwkerk et al., 2001).

The average rate of adherence varies by the method used to assess it and the group studied. In one prospective study, 140 individuals in a public U.S. hospital HIV clinic were followed for one year after initiation of HAART. The investigators assessed adherence using three methods and calculated a composite adherence rate of only 71%. Only six percent of the patients took at least 95% of their medications, the optimal level for durable virologic and clinical success (Golin et al., 2002). Studies of different groups of HIV-positive individuals in the United States and abroad generally show similar, suboptimal rates of adherence (Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Knobel et al., 2001; Murri et al., 2000; Walsh, Mandalia, & Gazzard, 2002). Rates of adherence are known to decline over time. Most patients taking HAART, regardless of

their background or life situation, will encounter difficulties with adherence at some point (Howard et al., 2002; Mannheimer, Friedland, Matts, Child, & Chesney, 2002).

Inadequate adherence may eventually undermine the dramatic improvements in HIV-related health parameters seen in resource-rich countries and the expected response in developing countries as HAART becomes more widely available. Not only can nonadherence negatively impact clinical outcomes, it can add significantly to the cost of care. It was, however, the recognition that nonadherence results in transmittable forms of drug resistant strains of HIV that brought attention to the problem rather than suboptimal clinical outcomes (Chesney, 2006).

Although most experts accept that adherence to antiretroviral medication is critical to the effectiveness of HIV treatment (Bangsberg et al., 2000; Haubrich et al., 1999; Liu et al., 2001), few rigorously designed studies have documented the efficacy of interventions to improve adherence to ARV treatment (Williams et al., 2006). While the potency of current therapeutic options for treatment of HIV disease has decreased morbidity and increased survival, imperfect adherence to HAART remains a major cause of treatment failure among patients with HIV disease (McNabb et al., 2001) (Palella et al., 1998; Paterson, Potoski, & Capitano, 2002).

Impact of Adherence

Highly active antiretroviral therapy has resulted in a longer life during the chronic stage of HIV infection. The Swiss HIV cohort study initially documented this trend, showing an increase in the survival rate from 19% in 1991 to 62% in 1996 (Egger et al., 1997). Recent projections published in 2006 estimated that the life expectancy of someone currently beginning care for treatment of HIV is at an all-time high of 24.2

years (Schackman et al., 2006). It is imperative that research be conducted to more fully understand adherence and to identify evidence-based interventions that can be developed and implemented to improve patient outcomes in people living with HIV disease.

Factors Associated with Nonadherence

Adherence to medication is a complex behavior which is influenced by many factors related to the patient, the prescribed treatment, the disease state, the healthcare provider and patient-healthcare provider relationship, and the healthcare system. Many studies have yielded discordant results, making it difficult to achieve consensus on modifiable barriers and predictors on which adherence intervention strategies should be designed (Ammassari et al., 2002). Some of these factors are immutable such as age, income, literacy, and the patient's social milieu while other factors are potentially alterable, such as depression, substance abuse, regimen complexity, medication side effects, and the therapeutic relationship between patient and provider.

Patient Factors

Patient factors affecting adherence include the sociodemographic factors of age, gender, race/ethnicity, income, education, literacy, housing status, insurance status, and risk factor for acquisition of HIV infection. Psychosocial factors typically encompass mental health issues, substance use, social climate and support, knowledge and attitudes about HIV and its treatment). Additionally, patients have identified many diverse reasons for missing their medications. Gifford and his colleagues (2000) found that organizational difficulties (e.g., too busy, forgot, away from home, change in routine) and emotional issues were the most common reasons for missed doses.

Conflicting results have been reported regarding the association between sociodemographic factors and adherence behavior. When an association was found, the direction was consistent: younger age, non-white race/ethnicity, lower income, lower literacy, and unstable housing were negatively associated with adherence in resource-rich settings. Gender, educational level, insurance status, and HIV risk factors generally were not associated with adherence behavior (Altice, Mostashari, & Friedland, 2001; Gifford et al., 2000; Golin, Isasi, Bontempi, & Eng, 2002; Haubrich et al., 1999; Holzemer et al., 1999; Kleeberger et al., 2001; Mannheimer, Friedland, Matts, Child, & Chesney, 2002; Paterson et al., 2000).

Psychosocial Factors

More consistent associations were found between certain psychosocial factors and adherence behavior. Common predictors of less than adequate adherence include untreated depression, other psychiatric morbidity such as anxiety and bipolar disease, stressful life events and lack of social and family support (Ammassari et al., 2001; Cinti, 2000; Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Holzemer et al., 1999). Active substance abuse including cocaine, marijuana, amphetamines, sedatives, and moderate to heavy alcohol consumption have also been inversely linked to adherence (Golin et al., 2002). Patients who are unable to correctly identify their drug regimen or describe the relationship between adherence and drug resistance are also more likely to be nonadherent. Belief in the efficacy of the medication and the presence of social support systems has been positively related to adherence to HIV (Ammassari et al., 2002) (Miller et al., 2003; Stone et al., 2001; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003).

Treatment Related Factors

Factors related to the treatment regimen can impact adherence including the number of pills prescribed, complexity of the regimen including dosing frequency and food instructions and restrictions, convenience of the regimen, type of ARV agents prescribed (e.g. protease inhibitor vs. non-nucleoside reverse transcriptase-based), side effects associated with the agents and the ability to incorporate the regimen into an individual's daily routine (Bartlett, 2002; Chesney, 2000; Walsh, Mandalia, & Gazzard, 2002). In general, adherence declines with the emergence of side effects. Side effects associated with HAART are common and include transient events such as diarrhea, nausea and fatigue as well as longer-lasting adverse effects such as metabolic disorders including diabetes and lipid disorders, lipodystrophy and neuropathy (Chesney, 2003). With regards to HAART, side effects are the primary cause of nonadherence and account for more regimen changes than do treatment failures (Ammassari et al., 2001).

The association between the number of doses per day and patient adherence is well described, with adherence declining as dosing frequency increases (Bartlett, DeMasi, Quinn, Moxham, & Rousseau, 2001; Claxton, Cramer, & Pierce, 2001). High pill burden has been reported as a primary reason for missing or discontinuing HAART (Bartlett, DeMasi, Quinn, Moxham, & Rousseau, 2001; Trotta et al., 2002). With the continued development of newer antiretroviral treatment agents, attention has focused on improving the efficacy, convenience and tolerability of medications with particular emphasis placed on reducing pill burden and dosing frequency. Data are emerging that demonstrate a positive association on adherence with once daily HAART regimens (Johnson et al., 2006).

Bartlett (2001) identified pill burden as the most significant predictor of HAART response. Since that time, treatment regimens have continually been simplified. In 2006, a one-tablet, once-daily HAART regimen became available and greatly reduced the scheduling requirements and pill burden associated with HAART (U.S. Food and Drug Administration, 2006). In a meta-analysis of 23 clinical trials involving 3,257 patients to determine predictors of virologic suppression, researchers found pill burden to be the most significant predictor of antiretroviral response (Stone et al., 2001). Although once-daily regimens demonstrated improved attainment of virologic control in two large RCTs that compared once-daily with twice-daily regimens, it is not clear if the benefit seen with once-daily HAART resulted from increased potency of the regimens studied, better adherence, or both (Molina, Ferchal, & Rancinan, 2003) (Raffi, Saag, & Cahn, 2003; Saag, Cahn, & Raffi, 2002). Data from additional studies related to this issue are expected in the near future.

Stone et al. (2001) conducted a cross-sectional survey of women and found that self-reported adherence was better among patients with less complex HAART regimens due in part to the fact that patients' understanding of regimen dosing decreases as regimen complexity increases. Therefore, simplifying HAART regimens may have an important role in improving patients' adherence. Conversely, increasing complexity in the medication regimen is associated with decreasing patient adherence.

Disease Characteristics

Disease characteristics affecting adherence include the stage and duration of HIV infection, HIV-related symptoms and AIDS-associated opportunistic infections. Adherence rates are consistently lower for a long term, chronic illnesses and for asymptomatic conditions (Graney, Bunting, & Russell, 2003). Over time, even the most motivated patients may find it increasingly difficult to remain adherent (Ickovics et al., 2002).

Asymptomatic HIV-infected patients may be less adherent since the only immediate perceived effect of HAART may be deterioration in health status and well-being as a result of medication side effects and disruptions in daily routine. Certain patterns of behavior in patients with chronic, asymptomatic illness have been linked to nonadherence including not filling prescriptions, forgetting doses, taking incorrect doses, stopping medication too soon, and self-regulating the regimen to manage side effects (Ammassari et al., 2002; Chesney, 2003; Hubbard, 2006; Trotta et al., 2002).

Conversely, Williams (1999) found that adherence is frequently greater in patients with advanced HIV disease as the improvement in disease-related symptoms resulting from controlling viral replication with HAART often outweighs the adverse effects of treatment. Increased adherence was seen in patients with opportunistic infections. The researchers believed this was explained by the patients' desire for improved health and a stronger motivation to adhere. Several studies described a relationship between HIV-related symptoms and nonadherence (Holzemer et al., 1999; Wagner, 2002).

Holzemer and colleagues (1999) found that clients with higher symptom scores, particularly depression, were more likely to be nonadherent to medication, not to follow provider advice, and to miss appointments while those who reported having a meaningful life, feeling comfortable and well cared for, using their time wisely, and taking time for important things were both more adherent to their medications and more likely to follow provider's advice. They suggested that strategies to enhance adherence should include recognition and treatment of symptoms (particularly depression) and an understanding of clients' perceptions of their environment.

Patient-Provider Relationship and Social Support

Several studies have documented that positive relationships with friends, family and healthcare providers can impact adherence to medication. Researchers found that a positive patient-provider relationship can be an important motivating factor for taking and adhering to HAART. Factors that have been identified as strengthening patient-provider relationships include communication quality and clarity, compassion, willingness to include patients in treatment decisions, adequacy of referrals, and convenience of visiting the provider. Conversely, frustration for providers has been associated with lack of adherence to treatment, missed appointments, complexity of treatment regimens and medication side effects (Ammassari et al., 2002; Chesney, 2000).

Health beliefs, coping skills and rapport with healthcare providers have been correlated with adherence to HAART. Patients are more likely to be adherent if they have confidence in, and guidance from, their healthcare providers (Bertholon, Rossert, & Korsia, 1999; Holstad, Pace, De, & Ura, 2006). The patient's overall satisfaction and

trust in the provider and clinical staff along with the patient's opinion of the provider's competence, willingness to include the patient in the decision-making processes, the adequacy of referrals and the convenience of visiting the provider can affect adherence (Ammassari et al., 2002; Chesney, 2000; Stone et al., 1998).

Findings from two studies suggested an association between stressful life events and nonadherence (Gifford et al., 2000; Moatti et al., 2000). Lack of social or family support and poor self-efficacy have also been found to be an important risk factor for nonadherence (Altice, Mostashari, & Friedland, 2001; Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000; Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Murri et al., 2002; Stone et al., 1998). Ammassari and colleagues (2002) concluded that the presence of tangible and emotional support can reduce barriers and increase motivation for adherence.

Lucas et al. (2004) found that patients who kept medical appointments were more likely to be adherent to medication. Additionally these researchers found that adherence was associated with patients' understanding that suboptimal adherence leads to resistance and a recognition that taking all medication doses is critically associated with adherence. It has been suggested that members of the healthcare team work in partnership with patients and to involve representatives from the entire HIV community to strengthen collaborative efforts related to the promotion of adherence (Chesney, 2000).

Environmental Factors: The Healthcare System

Research addressing the relationship between the healthcare setting and adherence behavior are limited. Chesney (2000) found that aspects of the clinical setting can

positively impact adherence such as easy access to ongoing primary care and convenience in scheduling appointments, involvement in a dedicated adherence program, availability of transportation and child care services, comfort with the clinical environment, perceived confidentiality, and satisfaction with past experiences in the healthcare system. Conversely, dissatisfaction with experience in the healthcare system has been associated with nonadherence. Women studied by Powell-Cope and colleagues (2003) identified difficulty obtaining medication refills and concerns related to confidentiality as barriers to adherence.

Conclusions

Adherence to highly active antiretroviral therapy is strongly correlated with both immunologic and virologic success, as evidenced by decreased HIV RNA levels and increased CD4 lymphocyte counts. Unfortunately, achieving and maintaining high levels of adherence to complex HAART regimens can be very difficult (Bangsberg et al., 2000; Haubrich et al., 1999). The reasons for inadequate adherence are complicated and often involve many variables related to the medications, co-morbid health conditions, environmental barriers and psychosocial concerns. Consequently, successful HAART is often limited due to inadequate medication adherence (Carpenter, 1997; Knobel et al., 2001).

Experts in the field of HIV have come to consensus on the importance of adequate adherence to HAART (Bangsberg & Deeks, 2002) (Chesney, 2003; Paterson et al., 2000). Despite the importance of this subject, empiric research on adherence interventions for HIV-infected individuals is minimal. Simoni and colleagues (2003) described adherence research as being in the embryonic stage. In their 2004 adherence

supplement, the DHHS guidelines concluded that interventions to improve adherence for HAART are insufficiently characterized and understood, and additional research regarding the topic needed (National Institutes of Health, 2004). Berg and Arnsten stressed that adherence measurement is needed in clinical and research settings, and called for research to evaluate methods and provide recommendations for research and clinical care (Berg & Arnsten, 2006).

The importance of adherence is demonstrated by the integration of adherence recommendations into national consensus guidelines for the use of HAART antiretroviral therapy (National Institutes of Health, 2006). While more adherence research is called for, methodological barriers are evident. Uncertainty exists regarding the best measure of adherence in both clinical practice and in research settings. Patient report, pill counts, and provider estimates may overestimate adherence, while electronic methods such as the Medication Event Monitoring System (MEMS) frequently underestimate ARV adherence, are too costly, and are not practical for use in routine clinical care. Furthermore, the process of monitoring patients behavior when measuring adherence may act as an intervention that changes adherence (Turner & Hecht, 2001).

Statement of the Problem

Adherence to HAART has arisen as one of the most important issues in the effective treatment of HIV disease. The difference in long-term viral suppressive response between those who take their medicine correctly 90-95% of the time and those who do not, can be the difference between life and death (Paterson et al., 2000). The identification of effective and clinically practical adherence interventions could greatly

improve the response to treatment modalities. For this reason, it is critical to determine interventions that promote adherence.

Purpose of the Study

The purpose of this retrospective comparative study was to evaluate the effects of a structured adherence intervention (SAI) as a component of an existing antiretroviral access program on adherence to HAART and response to treatment as compared to usual care. In the structured adherence intervention providers closely monitored monthly HIV medication refills and provided structured adherence intervention when indicated. Patients receiving usual care were enrolled in a Medicaid-funded medication access program and did not receive ongoing medication refill monitoring and structured adherence intervention. Both patient groups received their ARV medications and outpatient HIV medical care from a single treatment center and pharmacy.

Specific Study Aims and Research Questions

Study Aim 1: To determine whether patients participating in the SAI program experienced higher levels of adherence compared to patients receiving usual care, controlling for adherence services and intervention, HIV disease-specific factors, ARV-specific factors, and sociodemographic factors.

Research questions:

1a. Is there a difference in self-reported adherence in subjects participating in the SAI program compared to those who receive usual care?

1b. Is there a difference in pharmacy refill adherence in subjects participating in the SAI program compared to those who receive usual care?

Study Aim 2: To determine whether patients participating in the SAI program experienced improved response to treatment compared to patients receiving usual care, controlling for HIV disease-specific factors, ARV-specific factors, and sociodemographic factors.

Research questions:

2a. Is there a difference in CD4 lymphocyte response in subjects participating in the SAI program compared to those who receive usual care?

2b. Is there a difference in HIV RNA response in subjects participating in the SAI program compared to those who receive usual care?

Hypotheses

1. Patients participating in the SAI will have higher levels of self-reported and pharmacy refill adherence compared to patients receiving usual care, controlling for covariates.
2. Patients participating in the SAI program will have better immunologic (CD4 lymphocyte) and virologic (HIV RNA) responses to HAART compared to those receiving usual care, controlling for covariates.

Significance of the Study

Although a great deal of progress has been made in the measurement of medication adherence in HIV disease and evaluation of adherence interventions, additional work is still needed. Ongoing research is needed to develop and validate accurate, practical and cost-effective methods for measuring adherence to HAART that can be used in both developing and industrialized countries. Study samples should

include more racial and ethnic minorities and women to more accurately represent the current population with HIV disease.

Despite the importance of adherence related to HAART, empiric research on adherence interventions for HIV-infected individuals is minimal. Although several researchers have studied self-reported and pharmacy refill adherence, there are no published studies of medication access programs that proactively monitor pharmacy refills and initiate adherence interventions when adherence deficiencies are identified. This study is designed to further the existing knowledge with relation to these additional variables. The findings will provide information on the effects of a programmatic intervention on medication adherence and response to treatment that can be used to inform policy decision making at the local, regional, and state levels.

Summary

This chapter presented the importance of adherence related to HAART and the need to identify effective interventions to foster adherence. High levels of adherence to HAART are necessary for optimal response to therapy. Optimal response to HAART results in improved viral suppression, improved immunologic response and functioning, and ultimately a decrease in morbidity and mortality. Nonadherence remains strongly associated with mortality (Wood et al., 2003). Limited research studies have identified effective interventions which can improve adherence.

CHAPTER TWO: REVIEW OF THE LITERATURE

Introduction

This chapter includes a review of research related to the measurement of adherence to HAART in HIV disease and interventions to increase or strengthen adherence to HAART. Although adherence to HAART is the strongest predictor of HIV viral suppression, drug resistance, disease progression and death in HIV-infected individuals, there is no standard approach to adherence assessment and intervention in routine clinical practice.

Definition of Adherence

HAART adherence researchers have yet to identify a standardized definition of adherence and few studies use consistent measures of adherence. Therefore adherence data must be interpreted with caution and comparison among studies is difficult (Hill, Kendall, & Fernandez, 2003; Powell-Cope, Toney, & Montano, 2001). One study may define adherence as the percentage of prescribed doses taken within two hours of scheduled dosing time over a 1-week period according to electronic data monitoring (EDM) while another may operationalize adherence as the percentage of prescribed doses taken in the last month according to self-report. Adherence studies are also inconsistent with regard to measurement of clinical outcomes. Some studies reported immunologic effects in terms of CD4 lymphocyte response while others reported virologic outcomes in terms of HIV RNA response. Some studies reported both immunologic and virologic

outcomes while others do not address either of these outcome measurements (Simoni, Pantalone, Frick, & Turner, 2005). Holzemer et al. (1999) even expanded the concept of adherence beyond only medication adherence to include following clinician instructions and missed appointments.

Measurement of Adherence

Adherence to HAART is a complex issue involving social, cultural, economic and personal factors. This complexity makes it difficult to identify a reliable and valid single measure of adherence that is appropriate for all settings (Chesney, 2006). Research and clinical care have also been hindered by the lack of an inexpensive, quick and accurate method to measure adherence (Dunbar-Jacob & Mortimer-Stephens, 2001). Chesney (2006) argued that it may be impossible to develop a "gold standard" definition of adherence and a standard measurement of adherence as the HIV epidemic is too diverse throughout the globe.

Introduction

Clinical studies employ a number of methods, alone or in combination, to measure medication adherence. A number of studies have shown, however, that the objective measures used in research, although impractical for most clinical settings, are more sensitive than patient self-report for detecting medication adherence (Machtinger & Bangsberg, 2006).

Adherence is usually measured as either a categorical or continuous variable. Two common approaches to defining a categorical outcome are to consider whether the patient missed any pills over a specific interval (such as the last 3 or 7 days) or whether the patient has exceeded a set percentage of doses taken (usually 95%). This simplistic

dichotomous classification may not capture the complexity of adherence patterns such as adhering to timing of medication doses, medication-specific food requirements and taking the correct number of pills (Chesney, 2003).

Measuring adherence as a continuous variable is less common in the literature than a dichotomous measure. When measured as a continuous variable, adherence is usually defined as the proportion of prescribed doses taken as measured by an electronic drug monitoring device, self-report, or pill count. Adherence can also be measured as a continuous variable by obtaining the percentage of pills available for consumption by pharmacy refill records or the number of missed doses over a specified time period (Simoni, Pantalone, Frick, & Turner, 2005). Many published studies simply reported the criterion for adherence as meeting the minimum level of drug consumption such as greater than 70, 80, or 90% (Fogarty et al., 2002).

Adherence measurement is frequently classified as subjective (in the opinion of the patient) or objective (data recorded independently of the patient) (Orrell, 2005). Subjective approaches include self-report and self-administered questionnaires in which patients are asked to report the number of medications missed or taken based within a designated time frame. Objective methods include electronic data monitoring (EDM) devices, pill counts and pharmacy refill data. These various methods of measuring adherence will each be explored.

Subjective Measures of Adherence

Patient Self-Report

Patient self-report offers a relatively inexpensive, simple and non-intrusive means of incorporating adherence data into routine clinical practice and the research setting.

Self-report is useful due to the relatively low cost, ease of administration and flexibility of use in a variety of settings (Bangsberg, Bronstone, Chesney, & Hecht, 2002).

Although self-report is one of the most common methods of assessing medication adherence, inaccuracy may result due to imprecise or inconsistent questioning, patient forgetfulness and poor recall, or the patient's desire to provide socially desirable responses along with a desire to please the healthcare provider and prevent criticism. Recall periods are inconsistent between studies (e.g. number of doses missed over the last 3 days vs. the number of doses missed over the last 30 days). Consequently, when self-reporting methods are used to assess adherence, levels are frequently over-estimated.

Although patients who admitted they have less than optimal adherence are almost always truthful, the reverse is not always true (Miller & Hays, 2000b). Self-reported adherence was over-reported when compared to adherence measured by EDM in a study of 44 patients conducted by Melbourne and colleagues (1999). Using an investigator-designed questionnaire, patients self-reported an extraordinary amount of perfect adherence. Using EDM data, patients under-reported their degree of deviation from their stated dosing times.

A benefit of self-reported adherence measurement is the potential to reveal the reasons for missed or mistimed doses. Considering that clinical, behavioral and psychosocial factors are among the most important factors that influence adherence (Chesney, 2003), self-report provides an opportunity to identify factors that might negatively affect adherence (Powell-Cope, Toney, & Montano, 2001).

Researchers conducted a meta-analysis and found that self-reported measures reliably predicted clinical outcomes associated with adherence (Nieuwkerk & Oort,

2005). This information is consistent with earlier studies that examined the relationship between self-reported adherence and virologic outcomes, protease-inhibitor drug levels and other clinical outcomes (Kerr, Walsh, Lloyd-Smith, & Wood, 2005). While patient-reported adherence has been consistently associated with viral suppression, as has adherence measured by EDM and unannounced pill count, self-reported adherence questionnaires or interviews used in research may fail to identify 20% to 28% of nonadherent patients (Bangsberg, Bronstone, & Hofmann, 2002).

A number of studies have demonstrated a positive association between self-reported adherence and HIV RNA suggesting that self-reports may be a valid indicator of adherence (Haubrich et al., 1999; Montaner et al., 1998). Mannheimer and colleagues (2002) prospectively studied the correlation between self-reported adherence and successful response to HAART and found that a higher level of self-reported adherence over time was associated with better immunologic and virologic outcomes. While researchers concluded that self-reported medication adherence was a strong and independent predictor of virologic outcome, they also indicated that other methods of measuring adherence, such as the use of EDM, may allow for greater precision in measurement. A recent meta-analysis confirmed that despite significant study heterogeneity, the pooled association between self-reported HAART adherence and HIV RNA was statistically significant (Nieuwkerk & Oort, 2005).

The manner in which clinicians and researchers communicate with patients regarding adherence may impact the patient's response. Patients may provide more truthful information if the person collecting the data is not a direct member of the health care team or if the patient believes the data will not be reported to clinicians (Orrell,

2005). Questioning, whether verbal or in writing, that is carefully structured, nonjudgmental, culturally appropriate, and posed in a nonjudgmental manner and with the use of permissive language may elicit the most accurate and truthful self-report data (Mannheimer, Friedland, Matts, Child, & Chesney, 2002). An example might include: "Patients with complex medication schedules like yours often miss doses of their medications from time to time. Can you tell me how many doses you missed in the last week?" An alternative might include: "Of the seven doses of medication you were prescribed to take last week, how many did you actually take?" (Melbourne et al., 1999).

Patient self-report measures in the form of personal interviews or written questionnaires have many advantages including low cost, minimal participant burden, easy speed of administration, flexibility in terms of mode of administration and timing of assessment, and the potential to yield specific information about the timing of doses and adherence to food requirements. The specificity of self-report measures is high, i.e., patients' acknowledgment of nonadherence is generally credible (Bangsberg, Hecht et al., 2001). Self-report may not be feasible with some individuals such as the cognitively impaired (Simoni et al., 2006).

Written medication diaries may increase the accuracy of self-report in patients who have difficulty remembering their pill-taking history. A benefit is the relative low cost associated with this method. However, one study suggested that patients did not consistently complete diaries and when they did, they tended to fill in the information immediately before a clinic visit. In one study utilizing diaries, only 25% of patients returned their diaries as instructed (Miller & Hays, 2000b). Several other methods have been used to obtain self-report adherence levels including computer-assisted self-

interviews, visual analog scales, self-report instruments and questionnaires, and clinical assessment. Each will be briefly discussed.

Computer-Assisted Self-Interview

Computer-assisted self-interview (CASI) technology may be an efficient way of obtaining self-reported data to identify HAART regimen errors and to monitor adherence. CASI involves a computerized interactive structured interview that assesses patients' understanding of HIV medication regimens and adherence levels. To minimize literacy requirements, patients can listen to an audio track which reads the interview text that normally would be presented visually on the computer screen. Photographs or graphics, rather than antiretroviral names alone, can be used to facilitate visual recognition of a patient's HAART regimen. If performed in conjunction with a clinician appointment, the CASI data can be used to provide valuable teaching information as well as an assessment of adherence (Bangsberg, Bronstone, Chesney, & Hecht, 2002).

CASI is time-efficient and may help detect nonadherence due to regimen errors or missed doses. In one study, CASI adherence assessment identified serious HAART regimen errors in up to 54% of patients. CASI-based adherence assessment can facilitate intervention by alerting clinicians to potential adherence problems, prompting a more detailed discussion of adherence during a clinical visit (Bangsberg, Bronstone, Chesney, & Hecht, 2002). An adherence CASI has several additional advantages over traditional self-report methods. Patients can be routinely and periodically assessed with a visual query of their understanding of, and adherence to, their HAART regimen with minimal use of clinician time. This may help to identify patients with regimen errors or in need of focused or intense adherence intervention. Although there are expenses associated with

initial start-up of this method, ongoing expenses are typically minimal. Web-based CASI adherence assessment can be performed to identify difficulties with adherence more rapidly than otherwise possible with assessments that are only performed during actual clinic encounters.

Visual Analog Scale

Kalichman and his team (2005) used a pictographic visual analogue scale (VAS) to assess medication self-efficacy in a low-literacy population and found that the scores were associated with behavioral measures of medication adherence and HIV RNA response. Visual analogue scales may be appropriate for patients with language challenges as well as those with reading limitations. Giordano and his team (2004) compared an investigator-administered VAS in conjunction with a more complicated 3-day medication recall instrument and unannounced pill counts in a group of marginally housed indigent patients who were on stable HAART regimens. The VAS demonstrated good validity compared to unannounced pill count and HIV RNA, performed as well as the 3-day recall instrument and was easier to administer and answer than other recall instruments.

The VAS method offers several advantages over the traditional recall method including decreased time requirement, ability to obtain data over a longer time frame and a lower response burden on the patient (Giordano, Guzman, Clark, Charlebois, & Bangsberg, 2004). Researchers compared the accuracy of patient recall of adherence over 1, 3, 7, and 30-day intervals. Although it was expected that shorter periods of time would result in the most accurate recall, researchers found that the 30-day VAS

performed slightly better than other measures of self-reported adherence over shorter periods of time (Bangsberg, Bronstone, & Hofmann, 2002).

Self-Report Instruments and Questionnaires

Several adherence measurement instruments have been reported in the literature primarily in the context of clinical research trials. Most adherence questionnaires ask patients to recall the specific number of missed medication doses over a certain time period such as the last 2-7 days. Patients are typically asked to recall day-by-day and medication-by-medication doses or missed doses. Table 2 summaries adherence self-report instruments.

Table 2

Adherence Measurement Instruments

Instrument	***Description***	***Population Studied***	***Reliability/Validity***
Adult AIDS Clinical Trial Group (AACTG) Adherence Baseline Questionnaire (Chesney et al., 2000)	9-page self-report of beliefs about medications, social support, missed or late doses, self-efficacy, psychological distress, health habits, alcohol and drug use, sociodemographic characteristics and a 20-item symptom index. Takes approximately 10 minutes to complete. Approximately 62 items.	HIV infected patients, 20% female, 30 non-white	No detailed information available. Authors believe the instruments "appear to be practical, acceptable to patients" and investigators and should prove useful for efficient collection of data describing adherence to medications within clinical trials populations."
Adult AIDS Clinical Trial Group (AACTG) Adherence Follow Up Questionnaire (Chesney et al., 2000)	6-page self-report of missed or late doses, medication doses, food requirements or special instructions, reasons why doses were missed and a 20-item symptom index. Approximately 47 items.	HIV infected patients, 20% female, 30 non-white	Highly significant association was seen between self-report of missed doses and detectable viremia. Several correlates of non-adherence were identified.
Community Programs for Clinical Research on AIDS (CPCRA) Antiretroviral Medication Self-Report (Form 646) (Mannheimer, Friedland, Matts, Child, & Chesney, 2002)	7 day global recall of amount of each medication taken (all, most, about half, very few, none). Number of items varies based on number of ARV agents. Includs checklist of 10 possible reasons why ARV doses were missed.	HIV infected patients, 20% female, 72% non-white.	Not reported.
Godin's Self-Reported Questionnaire Assessing Adherence to Antiretroviral Mediation (Godin, Gagne, & Naccache, 2003)	9 main questions of which 3 address nonadherence. Developed in French and English.	Predominantly HIV infected men who have sex with men	Not reported, although authors stated, "adequate psychometric properties" (Godin et al, 2003, page 329)
Morisky Medication Adherence Scale (MMAS) (Corless et al., 2005; Morisky, Green, & Levine, 1986)	4 brief yes or no questions that address barriers to medication-taking and permit the clinician to reinforce positive adherence behaviors	Limited use in HIV disease; primarily studied in patients with hypertension, asthma and hyperlipidemia	Internal consistency, $\alpha = 0.61 - 0.65$
Patient Medication Adherence Questionnaire Version 1.0 (PMAQ-V1.0) (DeMasi et al., 2001)	6 items assess medication-taking behaviors; 25 items assess barriers and motivators to taking medication	HIV infected patients, 85% male, 32% non-white.	Internal consistency, $\alpha = 0.79$
Pictographic Medication Self-Efficacy Scale (Kalichman et al., 2005)	Pictographic and color visual analogue scale for assessing self-efficacy for medication adherence. Uses 6 scenarios.	HIV infected patients, 36% women, 99% African-American	Internally consistent ($\alpha = 0.68$); stability (2-week test/retest $r = 0.63$); evidence for convergent and divergent construct validity.
Simplified Medication Adherence Questionnaire (SMAQ) (Knobel et al., 2002)	6 items based on Morisky scale	HIV infected patients, 72% male, 65% IDU	72% sensitivity; 91% specificity; likelihood ratio of 7.94 to identify nonadherent patients, compared with MEMS; Internal consistency, $\alpha = 0.75$; Inter-observer agreement 88.2%, kappa 0.74.

The Adult AIDS Clinical Trial Group (AACTG) developed both a baseline and a follow-up self-report adherence assessment instrument for use in clinical trials. These instruments have been included in a number of AACTG clinical trials to date and have been widely disseminated to investigators both in the United States and abroad (Chesney et al., 2000). The Community Programs for Clinical Research on AIDS (CPCRA) 7-day global recall adherence questionnaire produced adherence data that predicted biologic outcomes including HIV RNA and CD4 lymphocyte count. Adherence was associated with non-detectable HIV RNA levels, a change in HIV RNA levels and a change in CD4 lymphocyte counts over a 12 month period (Mannheimer, Friedland, Matts, Child, & Chesney, 2002).

Morisky, Green and Levine (1986) developed an instrument to assess adherence to hypertension therapy which also addresses barriers to medication-taking. This tool has been incorporated into several studies involving HIV-infected patients and demonstrated success within this population (Corless et al., 2005; Gao & Nau, 2000). Knobel et al. (2002) developed the Simplified Medication Adherence Questionnaire (SMAQ) to identify non-adherent patients and determined the instrument to be adequate in most clinical settings. The Patient Medication Adherence Questionnaire (PMAQ) assesses medication-taking behaviors and barriers to adherence with HAART. Self-reported adherence derived from this instrument predicted virologic outcomes but the authors suggested additional refinement of the dimensions is needed (Boyle, 2003; DeMasi et al., 2001).

Some researchers have either developed their own assessment tools or have modified versions of other instruments, thus complicating the ability to compare data

from different studies. Gau and Nau (2000) measured adherence using a Morisky-type scale and two other measures of self-reported adherence to evaluate accordance yet found discordant results. They recommend caution when comparing adherence rates between studies that use different methods for assessing adherence.

Using self-report, Hill et al. (2003) studied patients' definitions of adherence, beliefs about consequences of nonadherence and reasons for current and past adherence behavior. They identified three categories of adherence: 1) consistent adherers; 2) currently adhering but with prior nonadherence; and 3) currently not adhering. They also identified nine patterns of adherence: 1) takes medication very rarely; 2) alternates between long period of taking and not taking medication; 3) skips entire days; 4) skips doses; 5) skips one type of medication; 6) takes medication late; 7) does not stick to food requirements or restrictions; 8) adheres to a purposely modified regimen and 9) adheres to an unknowingly incorrect regimen. Noting that patients have definitions of adherence that may be quite different from the definitions used by clinicians, they suggested that adherence questionnaires and assessment tools need to reflect the diversity of patient beliefs and patterns of medication-taking to more accurately measure adherence or less than optimal adherence.

In a large meta-analysis Simoni and colleagues (2006) observed a robust pattern of association between self-reported adherence and HIV RNA. In 84% of recall periods, self-reported adherence was associated with HIV RNA based on odds ratios or simple measures of correlation. The association was statistically significant across a variety of self-reported measures, administration modalities, and recall periods. These findings are consistent with the conclusions of a meta-analysis of adherence studies performed by

Nieukerk and Oort (2005). The association between self-report and CD4 cell count was less consistent, a finding that was not entirely unexpected since HIV RNA and CD4 count generally correlate, but discordant results are common. They concluded that even brief self-report measures of HAART adherence can be robust.

Clinician Assessment

Studies examining healthcare provider abilities to predict their patients' adherence have been inaccurate and overly optimistic leading to the misidentification of nonadherent patients (Bangsberg, Hecht et al., 2001; Haubrich et al., 1999). Paterson (2000) found that physicians predicted adherence incorrectly for 41% of patients compared with nurses who predicted it incorrectly for 30% of patients.

Miller and colleagues (2002) found that clinicians overestimated medication adherence by almost 9% and inadequately detected poor adherence. Consequently, clinicians missed opportunities to intervene with appropriate adherence interventions. Miller and Hays (2000b) suggested that clinicians' subjective assessment of adherence may be as problematic as a patient's self-reported adherence. HIV care providers in routine clinical practice rarely predicted patient adherence. This often means that when health care providers do not use patient reports of adherence, they are leaving the most critical determinant of HIV treatment outcome to chance (Bangsberg, 2006).

Objective Measures of Adherence

In contrast to subjective measures, objective measures rely on data recorded independently of the patient (Orrell, 2005). The following objective measurement methods will each be reviewed: directly observed therapy, therapeutic drug monitoring,

biomedical examination, pill counts, electronic monitoring devices, and pharmacy refill data.

Directly Observed Therapy

One way of assessing adherence is participation in directly observed therapy (DOT) in which administration of each dose is directly monitored. DOT has been used in the treatment of tuberculosis for decades and was later applied to HIV treatment (Mitty, Stone, Sands, Macalino, & Flanigan, 2002). The first randomized controlled trial of community-based DOT in HIV care revealed significantly higher levels of self-reported adherence, higher CD4 lymphocyte response, and greater HIV RNA reduction than those not participating in DOT (Altice, Mezger, & Bruce, 2003). DOT programs, often modeled after those used in tuberculosis treatment programs, may not be practical in HIV care due to the large and growing numbers of HIV-infected patients since these programs are labor intensive, expensive and can be perceived as intrusive (Liechty & Bangsberg, 2003). While DOT may be more feasible with the increasing number of once a day HAART regimens, many of these daily regimens are administered at bedtime which increases the impracticality of DOT for this group of patients.

Therapeutic Drug Monitoring (TDM)

Monitoring of plasma and urinary drug levels has been proposed in clinical and research settings. Serum levels of some drug metabolites provide evidence that individuals are taking medication but they do not provide specific information about the number of doses missed or taken, individual patterns of missed doses, or adherence to a medication based on a time schedule. This method is prone to wide individual variation in drug pharmacokinetics related to the properties of drugs, drug-drug interactions and

variations in drug absorption. Moreover, drug levels may only reflect recently taken medication doses rather than long-term patterns of drug levels (Miller & Hays, 2000a). Low drug levels have been associated with self-reported nonadherence and virologic failure (Murri et al., 2000; Nieuwkerk et al., 2001). TDM also is limited by a lack of technologic standardization of assays as well as limited general availability of the laboratory assays (Acosta & Gerber, 2002).

Some researchers have attempted to exploit the biologic changes induced by antiretroviral agents to indirectly measure adherence. Stavudine and zidovudine can raise the mean corpuscular volume, didanosine can alter uric acid levels and both indinavir and atazanavir can increase bilirubin levels. While these data provide some degree of objective measurement, they are only marginally sensitive and specific markers of medication adherence and provide little information about individual patterns of missed doses (Cinti, 2000; Miller & Hays, 2000a).

Biomedical Examination

Laboratory measurement of CD4 lymphocytes and HIV RNA levels has been used as indirect measures of adherence. Wood and his colleagues (2004) determined that adherence was the strongest independent predictor of an increase in CD4 lymphocyte count after beginning HAART therapy. Unfortunately, biomedical markers including CD4 lymphocyte cell counts and HIV RNA levels do not always correlate with adherence levels. Patients can have a drug-sensitive virus and be adherent to their HAART regimen yet still experience HAART failure due to the development of drug-resistant HIV strains, drug interactions and unfavorable pharmacokinetic properties (Miller & Chang, 2002). Additionally, laboratory testing can be expensive. Laboratory measures may be

considered more useful when used in combination with other adherence measures such as pill counts, self-report assessments and EDM (Cinti, 2000).

Pill Counts

Pill counts frequently are used in conjunction with clinical drug trials and provide an objective means of assessing the number of pills removed from the bottles. Pill counts are easy and inexpensive to perform (Miller & Hays, 2000b). Disadvantages of pill counts are that they can be time consuming for clinical and research staff; they do not guarantee that the pills were taken as prescribed; patients may knowingly empty the bottle prior to the visit in anticipation of a pill count; they may forget to bring bottles to the clinical site; and some may perceive pill counts as intrusive (Berg & Arnsten, 2006).

Unannounced pill counts may provide a more accurate assessment of adherence rates than self-report. In one study this method was more predictive of HIV RNA than self-reported adherence measures and performed well compared to electronic data monitoring using computerized medication caps (Bangsberg et al., 2000). Unannounced pill counts may not be practical in many settings since home visits are usually required.

Electronic Monitoring Devices

Computer-assisted electronic drug monitoring devices, also commonly referred to as electronic data (and sometimes drug) monitoring (EDM) devices, are frequently used in research settings and to a lesser extent clinical settings. Small electronic chips embedded in the caps of pill bottles record each time a bottle is opened or closed and the length of time the bottle is open. Data is downloaded to a personal computer periodically for analysis. One of the more common EDM products is the Medication Event Monitoring System (MEMS) (New York State Department of Health, 2001).

Data collected from EDM equipment has been found to correlate highly with concurrent HIV RNA (Samet, Sullivan, Traphagen, & Ickovics, 2001). Limitations related to EDM include expense and the possibility of under-reporting adherence in patients who elect to remove more than one dose at a time. Under-reporting may occur when patients remove medication to fill a pill box or remove extra doses in planning to be away from home for an extended period of time. EDM also assumes that the patient actually takes each removed pill. Over-reporting can also occur as pills may be removed but not swallowed and bottles may be opened without removing pills. EDM methods have additional drawbacks including inconvenience, patient dissatisfaction and confidentiality concerns (Mannheimer, Friedland, Matts, Child, & Chesney, 2002). EDM is rarely used in clinical practice due to the expense of the equipment.

Pharmacy Refill Monitoring

Pharmacy refill data can serve as an adherence measure by providing the dates on which antiretroviral medications were dispensed. This measure is based on a straightforward premise that when a patient does not receive timely refills of a drug from the pharmacy, he or she is either not taking medication between refills or is missing doses such that a given prescription lasts longer than it should (Turner, 2002). Researchers have studied the number of prescriptions picked up, timeliness of medication pickup and gaps in medication based on refill data. These measures are usually calculated based on the number of days' supply obtained divided by the total number of days in the period or the number of refills obtained divided by the expected number of refills over a given time period (Steiner & Prochazka, 1997). Low-Beer, Yip, O'Shaughnessy, Hogg and Montaner (2000) examined pharmacy dispensing data and found a significant linear trend

in viral suppression across ordered categories of adherence. Pharmacy refill adherence rates of 95% or greater were associated with high virologic success; success rates decreased sharply with decreasing levels of adherence to refills.

Several studies have used pharmacy data to assess adherence among patients with HIV disease. One study found that self-reported HAART adherence correlated with pharmacy dispensing records and predicted viral suppression at levels $\geq$ 97% (Fairley, Permana, & Read, 2005). Grossberg and colleagues (2004) demonstrated that adherence, as measured by time-to-pharmacy refill, was able to distinguish an HIV RNA impact among individuals self-reporting perfect adherence. Patients who were adherent to HAART as measured by consistent pharmacy refills for greater than 4 months were significantly more likely to achieve virologic control and immunologic benefit than were less-adherent patients (Maher et al., 1999). Using pharmacy-based adherence measures, Kitahata et al. (2004) determined that higher levels of adherence to HAART were significantly associated with longer time to virologic failure, greater increase in CD4 lymphotcyte count, and lower risk of progression to clinical AIDS or death. After controlling for other factors, patients with low adherence had over five times the risk of disease progression in patients with moderate adherence, or patients with high adherence.

Assessing refill records is non-intrusive and reduces the possibility of bias in the research process as subjects are usually not aware that their behavior is being monitored. However, like other measures of adherence, pharmacy refill pickup does not assure that the patient actually took the medication as prescribed (Miller & Hays, 2000b).

Combined Methods of Adherence Measurement

To address the limitations of any one measurement approach, some researchers have suggested that adherence measurement methods be combined (Kerr, Walsh, Lloyd-Smith, & Wood, 2005). The use of medication diaries with computer-assisted self-interviewing gave insight into patients' adherence patterns (Hugen et al., 2002). Self-reported adherence data has also been shown to enhance data obtained from electronic monitoring methods (Bangsberg et al., 2000).

Liu and colleagues (2001) examined different adherence measures applied to the same patient and found that different methods of measurement suggested different levels of adherence. Adherence was underestimated by EDM and overestimated by pill count and interview. Data obtained from EDM, pill counts, and interviews were subsequently merged into a composite adherence score (CAS). While adherence as measured by CAS, EDM, pill count, and interview were associated with achievement of undetectable viremia within six months of initiating HAART therapy, the CAS demonstrated the strongest predictive relationship. Although the summary measure combining several measures was more strongly related to a clinical response, they suggested a more practical measurement method is needed for clinical use.

Berg and Arnsten (2006) suggested that adherence is especially difficult to measure because it is composed of several distinct behaviors. Component adherence behaviors include obtaining refills, ingesting the right number of pills, ingesting pills within an effective dosing interval, and ingesting pills in accordance with any appropriate dietary requirements. Individual measures of adherence frequently measure just one single aspect of adherence behavior. This phenomenon of "construct under-representation" occurs when a measure fails to assess important dimensions of the

construct in question (Hubley & Zumbo, 1996). Although some adherence measures such as EDM provide the ability to measure several aspects of adherence, the data are not generally analyzed in this manner. EDM and other measures are vulnerable to another validity threat caused by measuring unrelated constructs. The term "construct irrelevant variance" is used when a measure contains excess variance attributable to unrelated constructs (Berg & Arnsten, 2006).

No single method has been established as the gold standard for measuring adherence. Each method has advantages as well as disadvantages. The HIV treatment guidelines published by the HIV Medicine Association of the Infectious Diseases Society of America suggested that once an adherence assessment method has been selected, it should be used consistently to monitor each patients' adherence at each visit (Aberg et al., 2004). Chesney (2006) indicated that it is unlikely that a single optimal measurement of adherence can be found as the reasons for measuring adherence vary based on whether the assessment is for research or clinical purposes and require further refinement based on the research questions being investigated or the clinical needs being addressed. Consequently, it is unlikely that a single optimal intervention can be developed because the reasons for nonadherence are as diverse as the populations affected by HIV disease.

In summary, there is no clear and universal method to rigorously measure individual patients' adherence. Rigorous adherence measurement requires interdisciplinary collaboration between social scientists and HIV researchers. Improving the measurement of HAART adherence would facilitate the development and evaluation of adherence-improving interventions with standardized and empirically tested adherence measures (Berg & Arnsten, 2006).

Measurement of Treatment Outcomes

The success as well as failure of HIV treatment can be evaluated using virologic, immunologic, and clinical criteria. Virologic indicators appear earliest after initiating HAART and are represented by a decrease (in the case of success) or increase (in the case of failure) in HIV RNA. Immunologic treatment success or failure usually occurs next and is measured by an increase (success) or decrease (failure) in the CD4 lymphocyte count. Although clinical treatment failure, if it occurs, usually becomes apparent much later, clinical success can often be assessed early after the initiation of HAART as many patients experience an improvement in HIV-related constitutional symptoms, such as weight loss, generalized lymphadenopathy, fever, and night sweats (Hoffman, Rockstroh, & Kamps, 2006).

Measurement of Virologic Outcomes

Virologic success is defined as a reduction of HIV RNA to below the level of detection. This is based on an understanding that the more rapid and greater the decrease in HIV RNA, the longer the therapeutic effect (Kempf et al., 1998; Powderly et al., 1999). Commercially available assays which measure HIV RNA vary based on the lower level of detection and dynamic ranges. The most common lower-level thresholds report HIV RNA levels as less than (<) 50 copies, < 75 copies and < 80 copies based on the testing methodology and equipment being used. While a lower level threshold of <50 HIV RNA copies is most common, there are no data suggesting less virologic success when HIV RNA is measured with alternative thresholds (Hoffman, Rockstroh, & Kamps, 2006). Table 3 describes the common HIV RNA testing methodologies.

Table 3

Quantitative Plasma HIV RNA Techniques

Technique	Test Name	Manufacturer	Dynamic Range
HIV RNA PCR (RT-PCR)	Amplicor HIV-1 Monitor Test version 1.5	Roche	< 50 – 750,000 copies/ml
Branched chain DNA (bDNA)	Versant HIV-1 RNA 3.0	Bayer	< 75 – 500,000 copies/ml
Nucleic acid sequence-based amplification (NASBA)	NASBA or NucliSens HIV-1 QT	bioMerieux	<80 – 3,500,000 copies/ml

Adapted from Bartlett & Gallant (2005)

HIV RNA is the most commonly used variable used by clinicians to assess patient measures of adherence but it is also affected by antiretroviral drug resistance and drug bioavailability (Wagner et al., 2001). Serial measurements of HIV RNA are routinely used to monitor the effectiveness or failure of therapy and help to determine if the beneficial effect of treatment is being maintained or lost. A change of $\geq$ 3-fold or $\geq$ 0.5 $\log_{10}$ copies/ml is considered significant (Bartlett & Gallant, 2005; Steinhart, Orrick, & Simpson, 2002).

Measurement of Immunologic Outcomes

Immunologic treatment success is broadly defined as an increase in the CD4 lymphocyte count. It is difficult to individually predict the immunological success of therapy for patients on HAART as it varies significantly from one person to another. Although individual research studies may have precise operational definitions of immunologic success, no standard definition exists (Hoffman, Rockstroh, & Kamps, 2006). Immunological treatment success is not always associated with maximal viral

suppression as even partial suppression can result in a significant CD4 lymphocyte response (Ledergerber et al., 2004).

Serial measurements of CD4 lymphocytes are routinely used to monitor the immunologic response to therapy. In the absence of HAART, the average rate of CD4 lymphocyte decline is 4% per year for each $\log_{10}$ HIV RNA copies/ml. There is a great variability in CD4 lymphocyte test results. For example, the 95% confidence range for a true count of 200 CD4 lymphocyte cells per millimeter^3 is 118-337 cells per mm^3 (Bartlett & Gallant, 2005). Several factors can influence the variability of CD4 lymphocyte counts including laboratory analytical variation and seasonal and diurnal fluctuations. CD4 lymphocyte counts are also used to stage HIV disease and guide prophylactic treatment. A CD4 lymphocyte count <200 copies/mm^3 indicates severe immunodepression and is a diagnostic marker of AIDS (Bartlett & Gallant, 2005; Steinhart, Orrick, & Simpson, 2002).

Measurement of Clinical Treatment Outcomes

Clinical treatment success is dependent on virologic and immunologic success and has been reported in numerous studies (Ledergerber et al., 2004; Salzberger et al., 1999). Clinical response is not always easy to assess as there is no way to show what might have occurred if treatment had not been initiated. Clinical success is usually evaluated based on either the absence of clinical endpoints such as AIDS-defining illnesses or death or an improvement in, or resolution of, HIV-related constitutional symptoms such as weight loss, generalized lymphadenopathy, fever, and night sweats (Bartlett & Gallant, 2005; Hoffman, Rockstroh, & Kamps, 2006).

Impact of Medication Adherence on Immunologic and Virologic Outcomes

Adherence to HAART has been shown to be an important predictor of virologic suppression and of clinical outcomes (Gross, Bilker, Friedman, & Strom, 2001; McNabb et al., 2001; Paterson et al., 2000). HAART adherence is the second strongest predictor of progression to AIDS and death, after CD4 lymphocyte count (Bangsberg, Perry et al., 2001; Garcia de Olalla et al., 2002; Hogg et al., 2002). In a meta-analysis of randomized controlled trials (RCTs) of interventions for adherence to HAART, Simoni and colleagues (2006) found that across 19 RCTs with more than 1800 participants, those who received an adherence intervention were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve undetectable HIV RNA levels as participants in comparison conditions.

CD4 lymphocyte response can be somewhat delayed following initial HAART initiation. For this reason, many experts believe that HIV RNA is the best measure of therapeutic response to HAART (Nieuwkerk & Oort, 2005). Bartlett and Gallant (2005) believe that the CD4 lymphocyte response is the best clinical prognostic indicator.

Adherence Interventions: Review of Studies

Introduction

Increasing recognition that medication adherence is a determinant of treatment outcomes has generated a number of studies investigating methods to support and improve adherence. While early research studies on this topic were primarily based on small pilot and feasibility studies and had minimal empiric validity, there has been an increase in the number of RCTs with adequate sample sizes emerging over the last few years (Simoni, Pearson, Pantalone, Marks, & Crepaz, 2006). In general, patients who

receive interventions for adherence are more likely to achieve higher levels of adherence and are more often able to achieve undetectable HIV RNA levels than participants in various controlled conditions (Chesney, 2006). Adherence interventions are cost-effective, and are likely to provide long-term survival benefit to patients (Freedberg et al., 2006).

This section will review and summarize studies related to HAART adherence interventions. Interventions will be categorized as 1) patient education and counseling strategies; 2) directly observed therapy; and 3) adherence devices and reminders. Studies are often characterized as: 1) cognitive (designed to teach, clarify, or instruct); 2) behavioral, such as those designed to shape, reinforce, or influence behavior; or 3) affective, such as those designed to optimize social and emotional support.

Patient Education and Counseling Interventions

The majority of adherence interventions reported in the literature involve dedicated time with patients to plan for and support medication adherence. The frequency and nature of these interventions varied, but those that appeared effective were characterized by an initial education session followed by ongoing sessions maintained regularly over the course of treatment (Machtinger & Bangsberg, 2006). These studies typically involved cognitive interventions or educational interventions targeting patient knowledge of drug therapy and employed methods such as counseling by a nurse educator, clinical pharmacist, or physician. Cognitive interventions typically provided general information such as dosing instructions, medication description, drug interaction information or general information about HAART options.

A wide range of behavioral strategies have been implemented including the use of pillboxes, using a register to record administered medications, role-playing medication schedules and schedule adjustments, using behavioral problem-solving groups, teaching self-monitoring skills, and identifying risk factors for nonadherence. Some studies used a combination of interventions including cognitive and behavioral methods such as describing dosing instructions and graphs of HIV RNA levels or educational sessions with an adherence counselor and a weekly pill container. Some studies contained three interventions including cognitive, behavioral, and affective techniques.

Several published studies have tested educational interventions involving healthcare professionals teaching patients about their medications, the importance of adherence, and methods to strengthen adherence. While several researchers found that educational interventions had a sustained impact on adherence (Goujard et al., 2003), others found minimal or no effect (Rawlings et al., 2003; Remien et al., 2005). Virologic and immunologic impact was inconsistently observed. Adherence measurement methods also varied among these studies with EDM and self-report being most common. One researcher utilized cue-dosing (timing doses around meal times or regular daily activities) and monetary reinforcement to remind patients to take their medications and observed an improvement in adherence that was not sustained and returned to baseline with discontinuance of the intervention (Rigsby et al., 2000).

Two studies examined the effect of pharmacist-led adherence sessions (Haddad et al., 2000). Although patients who received the intervention self-reported higher levels of adherence, virologic improvements were only seen in one study (Rathbun, Farmer, Stephens, & Lockhart, 2005). Knobel (1999) administered individual advice regarding

adherence and the effect was measured with structured interview and pill counts. Those who received individual counseling had significantly better adherence rates than those who did not, but there was no significant difference in virologic response.

Several studies have tested motivational interviewing and cognitive-behavioral problem-solving approaches to improve adherence. Adherence was consistently higher in patients who received these interventions. While Safren et al. (2001) found little difference between patients that received a single intervention session compared with patients who simply maintained a pill diary and completed an adherence questionnaire, patients who received motivational interviewing led by nurses reported higher medication adherence than those receiving usual care and were more likely to follow the medication regimen as prescribed by their health care provider (DiIorio et al., 2003).

In another study, patients received 10 sessions of cognitive-behavioral stress management and expressive supportive therapy (Jones et al., 2003). Participants were assessed on self-reported medication adherence over seven days along with coping strategies and beliefs related to HAART. Patients with low baseline adherence that received the intervention significantly increased their mean self-reported adherence by approximately 30%. Those in the usual care group showed a non-significant increase in adherence. After receiving monthly cognitive behavior therapy sessions over a one year period, Weber (2004) found that patients' mean adherence as measured by EDM was similar between the intervention and standard care group. While the proportion of patients with adherence levels $\geq$ 95% was significantly higher in the intervention group, virologic outcomes in both groups were similar.

Smith, Rublein, Marcu, Brock and Chesney (2003) examined the effect of a self-management intervention based on feedback of adherence performance and principles of social cognitive theory on adherence. Individuals in the self-management group were significantly more likely to take 80% or more of their doses each week than individuals in the control group as measured by EDM.

In summary, some improvement in adherence has been seen with education and counseling-based interventions but the results were inconsistent and frequently diminished when the intervention was terminated. Significant immunologic and virological improvements were inconsistently observed.

Directly Observed Therapy

Directly observed therapy (DOT) has been studied as an adherence intervention based on its successful use in treating nonadherent tuberculosis patients. Fischl (2001) and her team compared patients receiving DOT in a correctional facility to those receiving standard outpatient clinic services and found that patients who received DOT had a significantly higher chance of achieving undetectable HIV RNA than those that received standard clinic care.

Altice, Mezger and Bruce (2003) compared DOT for once- daily dosing, modified DOT (twice-daily dosing in which one dose was give via DOT) and standard care. The patients receiving DOT had significant improvements in three-day self-reported adherence, six-month median CD4 lymphocyte response, and six months median reduction of HIV RNA. In another study, pregnant women who were identified as being at very high risk for HAART nonadherence and consequent mother-to-child transmission

were given DOT during the third trimester of pregnancy. Clinical outcomes of no perinatal transmission of HIV, suppression of HIV RNA, and receipt of appropriate antiretroviral agents during labor were similar to those that received standard care (Bryant, Collingham, & Till, 2004).

While studies of DOT have resulted in improvements in clinical outcomes associated with HAART, DOT programs may not be appropriate for most clinical setting as they are expensive, labor-intensive and frequently perceived by patients as intrusive (Liechty & Bangsberg, 2003). Machtinger and Bangsberg (2007) believe that the best candidates for DOT are those with low motivational states who have experienced failure with less intensive adherence support and who have advanced HIV disease.

Adherence Devices and Reminders

A number of devices are available to help patients adhere to their medication regimen including medication organizers such as pillboxes, reminder devices such as alarm watches and pagers, and visual medication schedules. Golin and her team (2002) found that patients who used more adherence aids were more adherent. The manufacturers of electronic drug monitoring devices have even added clocks and alarms to their equipment to help remind patients to take their medication as prescribed (Miller & Hays, 2000a). Most devices are simple, inexpensive, and easy to integrate into the routine care of patients. Pill boxes allow patients to organize their doses of medication in a convenient location. They eliminate the need to carry multiple medication bottles and provide a means to verify whether doses have been taken. Clinicians can monitor for nonadherence if patients take pillboxes to clinical appointments. Some pharmacies

provide medications prefilled into weekly or monthly organizers (Machtinger & Bangsberg, 2006; Machtinger & Bangsberg, 2007).

While the success of these devices has primarily been reported based on clinical and field experience, several research studies have been conducted related to this area. McPherson-Baker et al. (2000) prospectively studied patients who participated in weekly sessions using pillboxes combined with monthly individualized adherence counseling. After five months, those receiving the intervention had a significant improvement in their adherence as measured by pharmacy refill data and fewer hospitalizations.

Because many patients cite 'forgetting' as a primary reason for missing doses of HAART, reminder devices such as alarms on watches, pagers and other electronic technology are recommended to provide multiple daily reminders (Chesney, 2000; Chesney, Morin, & Sherr, 2000). Andrade et al. (2005) measured the effect of a memory-prompting device combined with monthly adherence counseling on adherence to HAART in memory-intact and memory-impaired subjects in a prospective RCT. Mean adherence scores as measured by EDM did not differ between the intervention and control group. However, a subset of memory-impaired patients who received the intervention had significantly higher levels of adherence.

Safren and his team (2003) tested a customizable reminder system using web-based pager technology to increase and maintain adherence in patients with pre-existing adherence problems. After a two-week monitoring period with EDM, participants with less than 90% adherence were randomized to continue monitoring or to receive a pager. Compared to standard care, the group who received the pagers had greater improvements

in adherence through the first three months but adherence at the end of the study was still poor in both groups. Safren suggested that more intensive interventions are required for patients with pre-existing problems.

Visual medication schedules contain pictorial displays of HAART agents superimposed on calendars as visual reminders of which pills to take and at what times. Although not tested in patients receiving HAART, Schillinger (2003) found that these visual schedules improved outcomes in patients receiving anticoagulation therapy (another chronic disease state involving daily medication that requires high levels of adherence).

Qualitative Reviews and Meta-Analyses of HAART Interventions

The literature related to HAART adherence interventions has been reviewed several times. Early qualitative reviews indicated that reports were based primarily on small pilot and feasibility studies and offered few prescriptive guidelines with minimal empiric validity. While later reviews highlighted the improved rigor of the studies, considerable variation in sampling and assessment strategies, intervention components, and findings was noted (Simoni, Pearson, Pantalone, Marks, & Crepaz, 2006).

Fogarty et al. (2002) published the first comprehensive literature review all of published articles reporting interventions designed to increase adherence to HAART. Although 16 interventions were identified employing a wide range of behavioral, cognitive and affective strategies, only 11 included data on intervention and efficacy and the effects of these interventions were generally weak.

Simoni, Pantalone, Frick and Turner (2005) performed a meta-analysis of 15 randomized controlled trials related to adherence interventions and found some significant differences in either adherence or clinical impact between the intervention and control arms in 10 of the studies. They noted several significant concerns: 1) the findings were difficult to interpret due to the heterogeneity in the studies; 2) the duration of treatment intervention varied from 1 to 10 sessions with ongoing follow-up ranging anywhere from 1 day to more than 1 year; 3) the methods used to assess adherence varied from different types of self-report to EDM; and 4) measurement of immunologic and virologic response was uncommon. Improvement in adherence was not commonly sustained. Unfortunately, findings from similar interventions were inconsistent. For example, in two studies, cognitive-behavioral treatment was part of a successful strategy (Safren et al., 2001; Weber et al., 2004) but in two others it was not (Jones et al., 2003; Murphy, Lu, Martin, Hoffman, & Marelich, 2002). Simoni's (2005) review of the literature suggested a lack of empirical data necessary to make strong recommendations regarding the most efficacious way to improve adherence to HAART.

Simoni and her team (2006) conducted another meta-analysis to determine whether behavioral interventions addressing HAART adherence were successful in increasing the likelihood of a patients attaining 95% adherence or undetectable HIV RNA. Nineteen studies with a total of 1839 participants met their selection criteria of describing a randomized controlled trial among adults that evaluated a behavioral intervention with HAART adherence or HIV RNA as an outcome. Random-effects models indicated that across studies, those who received an adherence intervention were 1.5 times more likely to report 95% adherence and 1.25 times more likely to achieve an

undetectable HIV RNA compared to participants who did not receive an intervention. The intervention effect for 95% adherence was significantly stronger in studies that used recall periods of 2 weeks or 1 month as compared to 7 days or less. They concluded that more research is needed to identify the most efficacious intervention components and the best methods for using them in actual clinical settings (Simoni, Pearson, Pantalone, Marks, & Crepaz, 2006).

Amico, Harman and Johnson (2006) performed a research synthesis of HAART intervention outcome studies published between 1996 and 2004. Effect sizes were calculated for each study outcome resulting in 25 immediate post-intervention outcomes and an additional 13 follow-up effect sizes. They found small effect size (d = 0.35, odds ratio [OR] = 1.88) that varied considerably across studies. Interventions that specifically enrolled participants with known or anticipated problems with HAART adherence demonstrated medium effects on adherence (d = 0.62, OR = 3.07). Interventions that did not target their participants on similar criteria had small effects (d = 0.19, OR = 1.41). Adherence improvements showed no tendency to decay with time. The authors concluded that adherence intervention outcome studies must carefully delineate their target populations because defining individuals as "on HAART" does not provide the level of specificity needed to design and implement effective adherence interventions.

Given the relatively small effects observed from studies of single adherence interventions and in an effort to expand the breadth of adherence issues addressed by these interventions, combinations of adherence interventions are suggested by many adherence experts. Studies of patients with other chronic diseases suggest that

approaches addressing only one factor related to adherence will not be as powerful as interventions addressing multiple factors (Miller & Hays, 2000a).

Despite the need for programs and procedures that support or enhance adherence to HAART, little evidence exists about the extent to which clinical practices have been able to incorporate adherence interventions into their routine care. Investigators conducted a survey of clinical care settings in New York and Connecticut and determined that the current standard of care is to provide only minimal levels of adherence services. They also found that ad hoc adherence support was frequently offered on an as-needed basis (Harman, Amico, & Johnson, 2005). These findings support the need for the ongoing development of adherence interventions that are easily translatable to real-life clinical practice.

In some cases an intervention can become the standard of care despite the empiric data demonstrating its efficacy. In these cases it may be considered unethical to assign patients to the control arm of a trial. For example, randomized controlled trials have provided evidence that behavioral interventions improve adherence to HAART. Such interventions are increasingly considered the standard of care, making additional randomized trials less likely (Petersen, Wang, van der Laan, & Bangsberg, 2006).

In the absence of conclusive empirical data, clinicians have frequently turned to adherence strategies recommended by experts which are based on limited data, research from adherence in other disciplines, clinical practice experience and demonstrated correlates of adherence (Simoni, Pantalone, Frick, & Turner, 2005). For example, the Best Practices Guide, published online by the American Public Health Association (Jani,

2002) proposes a practical four step approach in the management of adherence: 1) assess factors that may influence adherence and function as potential barriers; 2) develop and maintain a therapeutic alliance with the patient; 3) monitor the level of adherence using multiple measures; and 4) implement multiple targeted interventions to resolve barriers to adherence. Chesney (2003), Turner (2002) and the American Psychological Association (1997) offered similar adherence management guidelines and recommendations which are summarized in Table 4.

Table 4

Adherence Management Guidelines and Recommendations

Turner	APA	Chesney
Simplify and explain the treatment regimen.	Clarify the regimen.	Deliver an introductory statement.
Provide reminder devices.	Tailor it to individual lifestyles.	Confirm understanding of the regimen.
Discuss potential side effects.	Facilitate interaction with clinic staff.	Assess adherence.
Provide social support.	Identify and remove personal barriers to adherence.	Ask about reasons for missing doses.
Treat concomitant psychological disorders and substance abuse problems.	Refer patients with special needs such as substance abuse to appropriate treatment.	Ask about medication side effects or other problems.
	Enhance self efficacy: offer positive feedback for new skills, demonstrated problem-solving and ways to integrate the regimen into their lives.	
	Create a social environment conducive to adherence: enlist support from patient's social network and maintain support of the clinical team.	
Adapted from Turner (2002)	Adapted from APA (1997)	Adapted from Chesney (2002)

Summary

Improving adherence to HAART may require a combination of methods appropriate to the patient and clinical setting. Alterable factors known to impact adherence, such as depression, substance abuse, and the therapeutic relationship between patient and provider should be addressed in a proactive and ongoing manner. Adherence interventions should include dedicated educational and collaborative time with patients to

plan for medication adherence and to maintain necessary support and collaboration throughout the course of treatment. In this way, problems such as side effects can be addressed, medications simplified or changed if necessary, and adherence devices supplied as deemed appropriate. Most of the adherence intervention strategies studied to date have focused on factors directly related to patient behaviors. Other variables known to impact adherence have not been thoroughly studied including factors related to the healthcare provider, the patient-provider relationship, factors related to the treatment regimen or illness, environment factors and contextual factors (Simoni, Pantalone, Frick, & Turner, 2005).

As successfully tested interventions emerge in the literature, it is critical that the information be disseminated into clinical practice. The issue of efficacy versus effectiveness will need to be addressed because what works successfully in a research-based trial may not work in clinics which face challenges such as limited staff and resources as well as diverse patient populations (Simoni, Pantalone, Frick, & Turner, 2005).

CHAPTER THREE: METHODS

Introduction

This chapter presents the research methods and procedures for this study. It includes treatment conditions, background information related to the structured adherence intervention, the study design, description of the study population and setting, inclusion and exclusion criteria, data collection procedures, data management, and the data analysis plan.

Treatment Conditions

Overview of the Study

This retrospective comparative study compared treatment response, pharmacy refill adherence, and self-reported medication adherence between two groups of patients: those participating in an AIDS Drug Assistance Program (ADAP) and those participating in a Medicaid-funded medication access program. The ADAP served as a structured adherence intervention (SAI) based on procedural and administrative processes required by the state-managed program. Those patients receiving antiretroviral medications as part of the Medicaid-funded program were considered usual care as this program did not contain systematic procedural and administrative conditions which could impact adherence. A number of other variables can impact medication adherence including adherence interventions (adherence counseling, education, and aids), ARV-related factors, sociodemographic factors, and HIV disease specific factors. Figure 1 depicts the conceptual model developed to structure this study based on existing research findings.

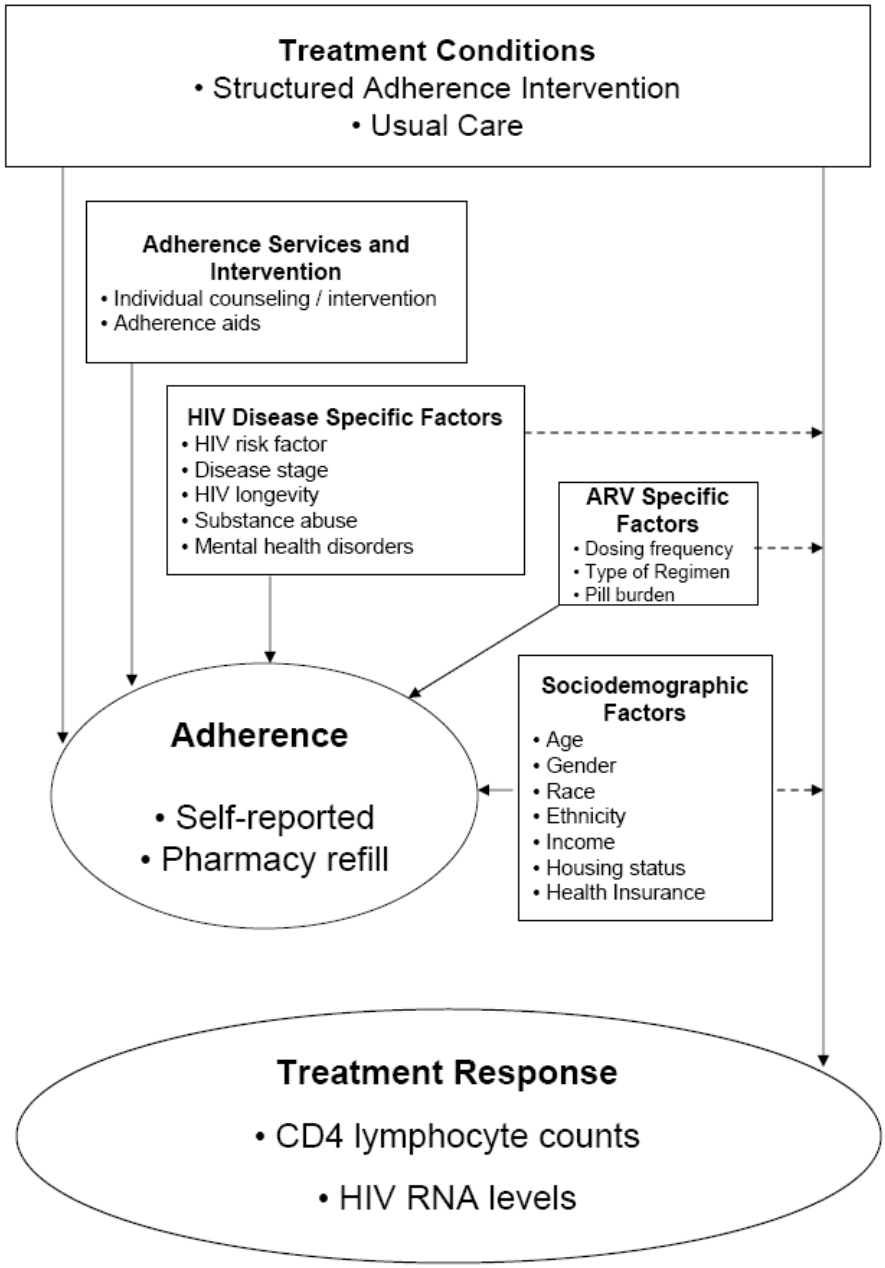

Figure 1. Conceptual Model for Evaluating the Effects of a Structured Adherence Intervention to HAART on Adherence and Treatment Response Outcomes.

Structured Adherence Intervention

Introduction: National AIDS Drug Assistance Program

The AIDS Drug Assistance Program (ADAP) is a federal program administered by each state to provide medications for the treatment of HIV disease. Eligibility to participate in the ADAP is based on the lack of adequate health insurance and financial resources necessary to cover the cost of medications. While some clients are enrolled in ADAP on a long-term basis, others participate temporarily while they await acceptance into other insurance programs. Each state AIDS Drug Assistance Program is unique in which medications are included in its formulary and how those medications will be distributed (Department of Health and Human Services, 2007).

Florida AIDS Drug Assistance Program

The ADAP for the State of Florida is centrally administered by the Bureau of HIV/AIDS in Tallahassee. The most populated counties within the state have local ADAP offices based in the respective county health department to serve the nearby residents. Smaller counties with lower numbers of HIV-infected patients are served via a central pharmacy in Tallahassee. Program policies and procedures are published in the ADAP Program Manual and serve as the operating standards for each ADAP office within the State (Florida Department of Health, 2007).

The goals of the Florida ADAP are to: 1) establish a program to provide therapeutics to treat HIV disease or prevent deterioration of health arising from HIV; 2) provide access to HIV treatments for low income, indigent persons who have no other resource to attain needed medications; 3) facilitate access to the program; 4) provide outreach to individuals with HIV and their families; and 5) provide program and

procedural technical assistance and guidance to county health departments to facilitate service to eligible persons. Two additional goals are explicitly related to adherence: 1) to help patients adhere to their treatment regimens and 2) to assist patients in avoiding interruption in ARV regimens (Florida Department of Health: Bureau of HIV/AIDS, 2003).

Many of the standards associated with the Florida ADAP are consistent with current recommendations and guidelines found in the Department of Health and Human Services (DHHS) treatment guidelines (National Institutes of Health, 2006). For example, clinical eligibility to start antiretroviral therapy with the Florida ADAP mirrors the recommendations of the DHHS for initiation of HAART. Similarly, the ADAP requires ongoing HIV RNA measurement and CD4 lymphocyte counts every three to four months to monitor response to treatment as recommended by the DHHS.

Although the ADAP is primarily a medication access program, administrative functions incorporate actions to monitor and reinforce adherence to HAART. The Florida ADAP Program Manual addresses a number of issues related to HAART adherence which are summarized in Table 5.

Table 5

Adherence-Related Statements in the Florida ADAP Program Manual

1.	Any department-specified or local health department adherence policy and/or procedure must be followed in educating and counseling the patient about taking medications.
2.	If there are problems with adherence, especially if a change in the HAART regimen is due to nonadherence, the patient's case manager and healthcare provider should be notified.
3.	Patients in the Florida ADAP may be disenrolled if the patient fails to pick up medications for more than 60 days and or is refusing to adhere to the medication regimen despite counseling and supports or other assistance offered. This decision should be made with the treating healthcare provider's input and guidance.
4.	Patients are responsible for picking up their medications on time each month before they run out.
5.	It is the goal of the ADAP to help patients adhere to their treatment regimens.
6.	Patients have to cooperate in picking up medication and providing required information as requested or required.

Adapted from Florida Department of Health: Bureau of HIV/AIDS. (2003). AIDS Drug Assistance Program Manual (ADAP). Tallahassee: Florida Department of Health.

The Florida ADAP Program Manual also addresses patients who are nonadherent to HAART. Nonadherence is defined as not picking up HAART agents from the pharmacy within 35 days of the last pharmacy refill (Florida Department of Health: Bureau of HIV/AIDS, 2003). The statements in Table 6 summarize the process that ADAP staff is expected to follow when a nonadherent patient is identified.

Table 6

Florida ADAP Procedures Related to Nonadherence and Failure to Pick-up

1.	If the patient is five or more workdays late for a scheduled medication pickup: • An inquiry should be initiated to determine the reason for the delay in picking up medications. • The case manager and treating healthcare provider must be notified as soon as possible. • A determination should be made as to whether or not the patient has had an interruption in drug therapy. If the patient last picked up a 30 day supply of medication, and has not been back to pick up for 35 or more days, then there has been an interruption in therapy. • If there has been no interruption in drug therapy, the patient should be encouraged and assisted in getting his or her medications for the month. • If there has been an interruption in drug therapy of five or more days, a consultation with the treating healthcare provider should be made as soon as possible before the patient is allowed to pick up his or her medications for the month.
2.	Patients who report "borrowing" or using another patient's medications to continue their own treatment are still considered to have an interruption in therapy if medications were issued by the Department more than 35 days prior. • Patients who report using "leftover" medications in their possession also may have been nonadherent. • Patients should not be given medications until the healthcare provider has been consulted and has given approval to issue medications or other instructions.
3.	If the patient fails to show at all for three weeks to 30 or more days to pick up medications, the treating healthcare provider and case manager must be notified. • If the patient comes in for medication at this point, he or she must see the treating healthcare provider before being given medication. • If the treating healthcare provider states that an office visit is not needed or desired, and wants medication issued, give the patient medications and document the name of the healthcare provider's staff who gave the instruction to issue the medications.
4.	If the patient fails to show at all for 60 days or more, he or she should be closed out of the ADAP system. • Notify the case manager and the healthcare provider that the patient has not picked up medication for 60 days prior to closure. • If the patient shows up in 60 days and has not been closed, he or she must see the treating healthcare provider, have new labs, and obtain prescriptions.
5.	If the patient has missed 90 days or more of medication, has not already been closed out, and comes in, no medications can be given. • The patient must see the treating healthcare provider, provide new labs and obtain new prescriptions. • Notify the healthcare provider and the case manager that the patient has missed 90 days of medication.
6.	Documentation of contact with the patient and the healthcare provider must be placed in the patient record. • Patients who decide to stop drug therapy without the knowledge or consent of their treating healthcare provider should be advised to contact him or her. • Notice of therapy interruption should be given to the healthcare provider by the ADAP contact.

Adapted from Florida Department of Health: Bureau of HIV/AIDS. (2003). AIDS Drug Assistance Program Manual (ADAP). Tallahassee: Florida Department of Health.

The Florida ADAP is unique with their approach to closely and regularly monitor medication refill adherence as part of the program's standard of practice. ADAP staff records the date that patients pick up their medications from the pharmacy in each patient's record. The program provides a 30 day maximum supply of ARV medication. Prescriptions can be refilled 28-35 days after the previous prescription has been dispensed. Programmatic standards state that if the patient is five or more workdays late for a scheduled medication pickup, an inquiry should be initiated to determine the reason for the delay in picking up medications. The case manager and treating healthcare provider must be notified as soon as possible. A determination should be made as to whether or not the patient has had an interruption in drug therapy which they define as a time lapse of 35 or more days since the patient last picked up a 30 day supply of medication (Florida Department of Health: Bureau of HIV/AIDS, 2003).

If there has been no interruption in drug therapy, the patient is encouraged and assisted in getting his or her next supply of monthly medications. If there has been an interruption in drug therapy of five or more days, a consultation with the treating healthcare provider is made as soon as possible before the patient is allowed to pick up his or her medications for the month. The treating healthcare provider can either approve additional medication dispensing or hold further medication dispensing. If dispensing is put on hold, the healthcare provider usually schedules a face-to-face meeting with the patient or requires that the patient schedule an appointment with the adherence specialist for additional assessment and intervention. It is this medication refill monitoring process that serves as the main monitoring component for the structured adherence intervention in this study.

Usual Care

Usual care in this study included patients that received their antiretroviral therapy from Florida Medicaid. Like the ADAP, this program also provided a 30 day supply of medication but did not contain procedural or administrative conditions which could impact adherence. Healthcare providers were not informed of missed or late pharmacy refills. It is theoretically possible that a patient could fail to pick-up any medication or could pick up medication refills erratically without the prescriber's knowledge.

Medication Adherence Assessment

Providers of the outpatient HIV treatment program monitor self-reported medication adherence at each clinic visit for patients participating in the ADAP and usual care programs. During the routine clinic intake process, a medical assistant asks each patient several adherence related questions and documents responses on a clinic-designed Medication Adherence Assessment Form. Although no validity or reliability testing has been performed on this specific assessment tool, self-reported adherence based on patient recall of the number of doses missed in the last 7-30 days has been reported in the literature as a valid indicator of adherence (Haubrich et al., 1999; Mannheimer, Friedland, Matts, Child, & Chesney, 2002; Montaner et al., 1998; Nieuwkerk & Oort, 2005). These self-report adherence questions are listed in Table 7.

Table 7

Medication Adherence Assessment Questions (Self-Report)

1.	How many doses of your HIV medication have you missed in the last week (7 days)?
2.	How many doses of your HIV medication have you missed in the last month (30 days)?
3.	Are you having any side effects from your HIV medications that interfere with your ability to take them on a regular basis?

Using the patient's response to the medication adherence assessment, the provider calculated an adherence rate for each patient. The monthly adherence rate was calculated as: (1 – [missed doses in the last 30 days / prescribed doses in the last 30 days]) X 100%. This percentage was documented in the patient's medical record and was subsequently entered into the LabTacker™ database by a data entry assistant.

Adherence Services and Interventions

The outpatient HIV treatment program employs a registered nurse in the capacity of adherence specialist. The adherence specialist was available to all patients that received care at the outpatient HIV treatment program including ADAP and usual care patients. While most patients are referred to the adherence specialist from their healthcare provider, patients can also self-refer to the specialist for assistance. ADAP staff also refers patients to the adherence specialist when they identify a perceived need for adherence assessment or intervention. Typical services and interventions provided by the adherence specialist are summarized in Table 8.

Table 8

Services and Interventions Provided by the Adherence Specialist

- General education related to the HIV disease process, HIV treatment medications and goals of treatment
- General and specific information related to ARV medications including dosing, timing, potential side effects and side effect management
- Medication scheduling assistance
- Education related to the importance of adherence, methods to prevent the development of ARV resistance, and pharmacy and medication refill processes
- Assessment of support systems
- Identification of potential barriers to adherence
- Support and counseling
- Prescription of adherence aids: pill boxes, timers, alarm watches

Adherence interventions may include the recommendation to use a pill box, the use of a programmable wristwatch which can display multiple digital messages to serve as reminders throughout the day, reminder telephone calls, education, counseling, and support. All services and materials are provided free of charge to the patient as they are provided by Ryan White Grant funding and donations.

Documentation of adherence assessment and intervention is documented in the clinic medical record along with the length of the visit in increments of 15 minute sessions. The adherence specialist maintains a Microsoft® Access database containing the patient's self-reported adherence percentage, number of visits for adherence counseling, length of time associated with each consultation, and interventions or aids that were provided or recommended to the patient.

Summary

The Florida ADAP includes a unique structured adherence intervention as a standard component within their medication access program. Pharmacy refill data is closely monitored by ADAP staff with the intent that patients will refill their medication on time, month after month. After picking up a month's supply of HAART medications, patients have approximately a one-week period to refill their next month's supply beginning at day 28 and ending at day 35. ADAP staff is in close contact with pharmacy, medical, and nursing staff to keep everyone proactively informed of patients that may have adherence deficits. Patients who do not pick up monthly refills within the appropriate timeframe are required to consult with the healthcare provider who may grant permission to resume medication or may require the patient to consult with the adherence specialist for further assessment and possible intervention. This structured adherence process served as the primary intervention in this research study.

Research Design

Study Design

This study used a retrospective comparative design to analyze secondary data. The study was designed to better understand the effects of a structured adherence intervention associated with an existing medication access program on adherence to HAART and response to HAART treatment compared to usual care. In the SAI group, providers closely monitored monthly HAART medication refills and provided structured adherence intervention when indicated. Patients in the usual care group were enrolled in a Medicaid-funded medication access program and did not receive ongoing medication refill monitoring and structured adherence intervention.

Study Population

The study population included all eligible patients participating in the Florida ADAP or in a Medicaid-funded medication access program who received HAART medications and outpatient HIV medical care from one single treatment center and pharmacy in west central Florida during the calendar year 2005. This time period was selected to minimize the influence of the implementation of Medicare Part D prescription medication coverage which was initiated in January 2006. The implementation of Medicare Part D prescription drug coverage had the potential to introduce additional confounders as the process was complicated for patients and staff, and resulted in difficulty in accessing medication for many individuals.

Inclusion Criteria

Included were all patients 18 years of age or older who completed a minimum of six consecutive months in the SAI or usual care program as the sole means of obtaining HAART medications during calendar year 2005 while on a consistent HAART regimen. All patients received their medication from the single pharmacy associated with the HIV treatment center.

Exclusion Criteria

Exclusion criteria included less than six months of consecutive participation in the SAI program or usual care program, alterations to the ARV regimen during the six-month period, or use of a pharmacy other than the on-site pharmacy.

Sample Size

This study used secondary data and the sample size was fixed. A preliminary query of the database suggested there were 1,355 potential subjects eligible for evaluation. Of these, 37% composed the usual care group while 63% composed the SAI group.

Since the exact number of patients meeting the inclusion criteria was not initially known, a conservative estimate of 50% (n=678) was considered for the purpose of establishing a power analysis. Results of the analysis using this conservative estimate should ensure that there is adequate power to conduct the proposed analyses. Results of the power analysis for more liberal estimates of 60% and 70% of the entire population are also provided to demonstrate the increased power available for the study should these situations be found in the data.

Power Analysis

Power estimates were derived for multivariable logistic regression, the least powerful and most complex of the analyses proposed in this study, thereby ensuring adequate sample size for all of the analyses in the study. Table 9 summarizes the estimated range of possible subjects and the respective power analysis associated with the estimate. Power analyses were also conducted using inclusion estimates of both 60% and 70%. The power estimates are displayed in Table 9.

Table 9

Power Estimates Based on Projected Sample Population

Database Population (N)	Percentage of Database Meeting Inclusion Criteria	Sample Size (N)	Power
1,355	50%	678	0.80
1,355	60%	813	0.86
1,355	70%	949	0.91

Because of the unique nature of this study, no data were found in the literature to suggest an appropriate effect size for this study. Therefore, effect size was chosen based on programmatically relevant changes. For this analysis a 10% improvement response to treatment by patients in the SAI program compared to those in the usual care program was identified as being programmatically relevant. Based on this assumption, a minimum sample size of 678 patients achieves a power of .80 at the .05 level of significance when expecting a .10 effect. The power analysis was conducted using the Power Analysis and Sample Size (PASS) statistical program (Hintz, 2001).

Setting

All patients considered for this study were enrolled in a comprehensive outpatient HIV care program in west central Florida. This center was established in 1989 and is the largest single public provider of HIV care on the west coast of Florida. The center serves approximately 1500 active patients. The clinic provides multiple services including medical and nursing care for patients with HIV disease along with pharmacy, dental, and social services.

Most patients were seen by their HIV care provider every one to three months. Most patients obtained their medications at the on-site pharmacy. All medications dispensed from the pharmacy were limited to a 30-day supply requiring prescriptions to be refilled on a monthly basis.

Study Variables

Dependent Variables

There are two outcome variables in this study: adherence (self-reported medication adherence and pharmacy refill adherence) and treatment response (CD4 lymphocyte response and HIV RNA response). Although adherence could be considered a proximal outcome variable that influences treatment response, it was considered as a terminal outcome in this study.

Self-reported medication adherence. Satisfactory adherence is defined as 90% or more of the pills prescribed in any regimen taken in accordance with the prescription plan. This is in agreement with the procedure from several other HIV medication adherence studies (Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Gross, Bilker, Friedman, & Strom, 2001). All self-reported adherence levels collected during the study period were assessed.

Pharmacy refill adherence. Pharmacy prescription refill data is used as a surrogate for medication-taking behavior and typically compares actual versus expected refills. Although this method does not guarantee that the medications were ingested, it does represent maximum probable adherence. Refill adherence is calculated as the percentage of times the index ARV agent (protease inhibitor or non-nucleoside reverse

transcriptase inhibitor) was refilled by the pharmacy within the 28-35 day timeframe during the study period.

CD4 lymphocyte response. CD4 lymphocytes were measured by four commercial laboratories using flow cytometry and hematology analyzers using fresh blood specimens. Test results indicated the number of CD4 cells per cubic millimeter of blood (Bartlett & Gallant, 2005). Immunologic response to HAART treatment was measured as the change in CD4 lymphocyte count from baseline to 6 months. A stable or increasing CD4 lymphocyte count is representative of successful HAART treatment.

HIV RNA response. Quantitative HIV RNA levels were measured by four commercial laboratories. Test results indicated the number of copies of HIV RNA per 1 mL of plasma (Bartlett & Gallant, 2005). Virologic response to HAART treatment was measured as the change in HIV RNA level from baseline to 6 months. An undetectable or decreasing HIV RNA level is representative of successful HAART treatment.

Independent Variables: Treatment Conditions

Group membership (SAI versus usual care) is the independent variable of interest in this study. The usual care group for this study included patients using Medicaid to fund their HAART at the same on-site clinic pharmacy. The Medicaid program did not include a specific adherence or prescription refill monitoring component. A maximum 30-day supply of medication was dispensed by the pharmacy at any one time. The SAI includes a number of standard procedures to monitor and strengthen adherence as described earlier.

Independent Variables: Covariates

Covariates include adherence services and intervention, ARV specific factors, self-reported medication adherence, pharmacy refill adherence, socio-demographic factors, and HIV disease specific factors.

Adherence services and intervention. The number of face-to-face visits with the adherence specialist during the study period, total length of time (in minutes) associated with these face-to-face visits, and prescription of adherence aids were assessed to compare the utilization of the adherence specialist's services between the groups.

ARV specific factors. Characteristics related to the HAART regimen were assessed including dosing frequency (once vs. twice daily), type of regimen based on index agent (non-nucleoside reverse transcriptase-based vs. protease inhibitor-based), and pill burden defined as the number of HAART pills prescribed per day.

Sociodemographic factors. Sociodemographic variables included age, gender, race, ethnicity, income level, housing status, and health insurance.

HIV disease specific factors. These clinical covariates included risk factor for HIV transmission, the number of years diagnosed with HIV infection, stage of disease (HIV vs. AIDS), and the presence of comorbid conditions known to impact HAART adherence including the presence of active substance abuse and active mental health disorders (depression, bipolar disorder and anxiety disorder).

Tables 10 and 11 list all variables considered in this study with detailed information related to the source of the data, frequency of measurement, operational definition and level of measurement.

Table 10

Variables, Definitions and Measurement (Part I)

	Source of Data	*Frequency*	*Operational Definition / Measurement*	*Level of Measurement*
Dependent Variables				
Medication Adherence: Self Report	LabTracker™	Month 0, 3 and 6	Self-reported number of ARV medication doses missed in the last 7 days. Adherence calculated as: (1 – [missed doses / prescribed doses]) X 100%. Average adherence >/= 90% = 1; <90% = 0.	Nominal
Medication Adherence: Pharmacy Refill	Pharmacy administrative database	Month 1, 2, 3, 4, 5, 6	Percentage of times the index ARV medication (PI or NNRTI) was refilled by the pharmacy within the 28-33 day timeframe during the six-month study period. Average adherence >/= 90% = 1; <90% = 0.	Nominal
Immunologic Response: CD4 Lymphocyte	LabTracker™	Month 0, 6	Change in value from month 0-6. No change or increase = 1; Decrease = 0.	Nominal
Virologic Response: HIV RNA	LabTracker™	Month 0, 6	Change in value from month 0-6. No change or decrease = 1; Increase = 0.	Nominal
Independent Variables				
Treatment Condition: Group Membership			Structured Adherence Intervention or Usual Care	Nominal
Covariates				
Sociodemographic Factors				
Gender	LabTracker™	Baseline	Male, Female, Transgender	Nominal
Age	LabTracker™	Start of study period	Age in years	Continuous
Race	LabTracker™	Baseline	White, Black, Asian/Pacific Islander, Native American (Alaskan), Multiple	Nominal
Ethnicity	LabTracker™	Baseline	Hispanic,	Nominal
Income level	LabTracker™	Baseline	< 100% FPL, 101-200% FPL, 201-300% FPL, >300% FPL	Ordinal
Housing Status	LabTracker™	Baseline	Permanent, Nonpermanent	Nominal
Health Insurance	LabTracker™	Each encounter	None, Medicaid, Medicare, Medicaid and Medicare, Hillsborough HealthCare	Nominal

Table 11

Variables, Definitions and Measurement (Part II)

	Source of Data	*Frequency*	*Operational Definition / Measurement*	*Level of Measurement*
HIV Disease-Specific Factors				
HIV Risk Factor	LabTracker™	Baseline	MSM, Heterosexual, IDU, MSM and IDU, Tissue/Blood Transfusion, Hemophilia, Perinatal, Unknown	Nominal
Disease Stage	LabTracker™	Baseline	Number of years the subject has been living with HIV Disease calculated as length of time from the first HIV-positive antibody test to the date of study entry	Interval
HIV Disease Status	LabTracker™	Once (study entry)	HIV or AIDS	Nominal
Active substance abuse	LabTracker™	Month 1,2,3,4,5,6	Yes, No	Nominal
Presence of MH disorder	LabTracker™	Month 1,2,3,4,5,6	Yes, No	Nominal
ARV Specific Factors				
Dosing frequency	LabTracker™	Baseline	One daily, twice daily	Nominal
Type of regimen	LabTracker™	Baseline	PI based, NNRTI based	Nominal
Daily pill burden	LabTracker™	Baseline	Number of total ARV pills taken per day	Continuous
Adherence Services and Intervention				
Number of Face-to-face adherence counseling visits	Adherence database	Month 1,2,3,4,5,6	Number of face-to-face visits with Adherence Specialist during study period.	Continuous
Time associated with face-to-face adherence counseling	Adherence database	Month 1,2,3,4,5,6	Total time in minutes of face-to-face visits with Adherence Specialist	Continuous
Adherence aids prescribed	Adherence database	Month 1,2,3,4,5,6	Yes/No	Nominal

Data Sources

Data were obtained from several electronic databases. This section will review the data sources, validity of data, methods associated with the process of obtaining de-identified data, data management, and security.

LabTracker™ (Ground Zero Software, 2007) software has been used as the primary database for clinical and administrative data for over four years. Sociodemographic data are reassessed at the patient's first outpatient visit in each calendar year by an advanced registered nurse practitioner or a physician. These data are subsequently entered and updated in the LabTracker™ system by two dedicated data entry assistants. Validity of data is continually monitored by a registered nurse and an advanced registered nurse practitioner who compare Lab Tracker™ data to medical record data and laboratory report forms to assure congruence. Accuracy of data is externally audited twice a year by two independent agencies to assure accuracy of recorded data and has consistently been 97-100% accurate when compared to medical record data and laboratory reports.

Pharmacy data was stored in the Pharmacy Management System (PMS) (Etreby Computer Company, 2007). Data was entered by clinical pharmacists and pharmacy technicians and was verified by the supervising pharmacist on an ongoing basis. Data is externally audited for accurateness annually and has consistently been 95-100% accurate.

A Microsoft® Access database contained the adherence specialists' utilization data associated with each patient. Data was entered by a registered nurse working in the capacity as an adherence specialist. Accuracy of the data is externally audited once a

year by an independent agency to assess accuracy of recorded data and has consistently been 98-100% accurate when compared to medical record data.

Data Collection Procedures

The health center administrator (HCA) at the clinical facility had complete access to the LabTracker™, Pharmacy Management System, and adherence specialist data bases. Information from all three data bases was initially linked by a four digit unique internal identification number that is used throughout the clinical facility. Once the HCA matched all data into one Microsoft® Excel file, the unique internal client identifier was replaced with a randomly generated study code using Microsoft Excel's random number generating program. Once the files were matched, the randomly assigned study code number was assigned as the only means of identification, and the matching algorithm was destroyed by the HCA.

The HCA provided the investigator with a Microsoft® Excel file containing all data elements and variables identified in this study. The resulting data file had no direct or indirect links that could identify any individual participant or group of participants.

Procedures

Institutional Review Boards

Approvals for Institutional Review Board (IRB) exemption were obtained from the University of South Florida's Office of Research, Division of Research Compliance IRB (Appendix A) and the Florida Department of Health IRB (Appendix B). Exemption from the IRB was granted because the study used existing data, documents, and records that were recorded without identifiers.

Letter of Support

A letter indicating support for the study was obtained from the director of the clinical facility.

Data Management

The Statistical Package for the Social Sciences (SPSS) version 15.0 was used for data analysis and data management. The data files were housed on a dual-password-protected network server at the clinical site with access only by the researcher and research assistant.

Missing Data

Incomplete or missing sociodemographic information, HIV disease specific factors, and ARV specific factors are highly unlikely as these elements are mandatory in the LabTracker database. While missing laboratory data is also unlikely, missing CD4 lymphocyte counts and HIV RNA levels will be imputed using the mean value of a subject's laboratory data collected in the study period.

Data Analysis Plan

The effects of the SAI will be assessed by testing two hypotheses. The following section describes the data analyses methods.

Hypothesis 1: Patients participating in the SAI will have higher levels of self-reported and pharmacy refill adherence compared to patients receiving usual care.

Hypothesis 2: Patients participating in the SAI program will have better immunologic (CD4 lymphocyte) and virologic (HIV RNA) responses to HAART compared to those receiving usual care.

Frequency distributions and descriptive statistics on all variables were performed to describe the study sample. There were two outcome variables in the study: adherence and treatment response.

A series of bivariate analyses were conducted to investigate the relationship between self-reported adherence and pharmacy refill adherence, group membership (SAI vs. usual care) and the covariates in the study. Variables found to be independently associated with adherence were considered for inclusion in a regression model. Logistic regression was performed on the outcome variables to test the effects of the treatment condition while controlling for adherence services and intervention, HIV disease specific factors, ARV specific factors and sociodemographic factors.

A series of bivariate analyses were conducted to investigate the relationship between CD4 lymphocyte response and HIV RNA response, treatment conditions (SAI vs. usual care) and the covariates in the study. Logistic regression was performed on CD4 lymphocyte response and HIV RNA response to test the effects of the treatment condition while controlling for HIV disease specific factors, ARV specific factors and sociodemographic factors.

Results of the study were reported as group data and no identifying information related to any person is presented.

Summary

Chapter 3 described the operating standards within the Florida ADAP that serve as a structured adherence intervention for patients receiving HAART and the Medicaid program that serves as the usual care group. The adherence assessment and intervention

processes, study design, population, setting, variables and data collection procedures were described. Finally, the data analysis plan was summarized.

CHAPTER 4: FINDINGS

This chapter presents the results of this study. Following a description of the sample and comparison of the study groups, the results of the bivariate and logistic regression analyses are reported.

Study Sample

The initial query of the LabTracker™ database suggested 1,355 potential subjects eligible for analysis. After inclusion and exclusion criteria were applied, 424 subjects were eligible for analyses. The SAI group included 204 subjects (48%) while 220 subjects (52%) in the usual care group were eligible for inclusion.

Subjects Excluded from Analysis

A total of 931 subjects did not meet inclusion criteria for this study. This number was higher than expected. The reasons for excluding these subjects are shown in Table 12. The primary reason for exclusion was not using the on-site pharmacy for ARV medication access. Patients with Medicaid or commercial insurance could select any community pharmacy to obtain medication. Although the usual care group in this study also had the potential to use any community pharmacy, subjects elected to use the on-site pharmacy at the study site.

Table 12

Subjects Excluded from Study

Reason for Exclusion	Number Excluded (%)
Not receiving antiretroviral therapy from the on-site pharmacy	565 (60.7)
Not prescribed antiretroviral therapy for at least 6 consecutive months	291 (31.2)
Missing data	49 (5.3)
Death during the first seven months of year 2005	26 (2.8)

Note: N = 931

In theory, these two populations should be similar with regard to socio-demographic, HIV disease characteristics and comorbid conditions. Sociodemographic variables were available for 547 of 565 patients who did not use the on-site pharmacy. These variables were examined using Pearson Chi-Square analysis to identify differences between the usual care group of subjects and the subjects excluded from the study because they did not use the on-site pharmacy. No significant differences were found between or among the two groups. This information is displayed in Table 13.

Table 13

Comparison of Sociodemographic Characteristics of SAI Group, Usual Care Group and Subjects Not Meeting Inclusion Criteria

	SAI n=204 Frequency (%)	Usual Care n=220 Frequency (%)	Excluded from Study n=547 Frequency (%)	Total N971 Frequency (%)
Gender				
Male	152 (74.5)	147 (66.8)	366 (66.9)	665 (68.5)
Female	52 (25.5)	73 (33.2)	181 (33.1)	306 (31.5)
Race				
White	123 (60.3)	106 (48.2)	264 (48.3)	493 (50.8)
Black	76 (37.3)	110 (50.0)	272 (49.7)	458 (47.2)
Other	5 (2.5)	4 (1.8)	11 (2.0)	20 (2.1)
Ethnicity				
Non-Hispanic	144 (70.6)	165 (75.0)	414 (75.7)	723 (74.5)
Hispanic	60 (29.4)	55 (25.0)	133 (24.3)	248 (25.5)
Age at time of study (years)				
18-29	22 (10.8)	9 (4.1)	24 (4.4)	55 (5.7)
30-39	52 (25.5)	42 (19.1)	107 (19.6)	201 (20.7)
40-49	79 (38.7)	99 (45.0)	245 (44.8)	423 (43.6)
50-59	46 (22.5)	52 (23.6)	128 (23.4)	226 (23.3)
> 60	5 (2.5)	18 (8.2)	43 (7.9)	66 (6.8)
Health Insurance				
Yes	69 (33.8)	219 (99.5)	539 (98.5)	827 (85.2)
No	135 (66.2)	1 (0.5)	9 (1.6)	145 (14.9)
Income Level (%FPL)				
<100%	124 (60.8)	168 (76.4)	419 (76.6)	711 (73.2)
101-200%	55 (27.0)	46 (20.9)	111 (20.3)	212 (21.8)
>200%	25 (12.3)	6 (2.7)	17 (3.1)	48 (4.9)
Housing Status				
Permanent	201 (98.5)	215 (97.7)	534 (97.6)	950 (97.8)
Nonpermanent	3 (1.5)	5 (2.3)	13 (2.4)	21 (2.2)

HIV disease specific characteristics and comorbid conditions were also compared between the subjects in the usual care group and the subjects excluded from the study.

These variables were examined using Pearson Chi-Square analysis to identify differences between the usual care group of subjects and the subjects excluded from the study because they did not use the on-site pharmacy. No significant differences were found between the two groups. Table 14 displays this information.

Table 14

HIV Disease and Comorbid Conditions - Characteristics of SAI Group, Usual Care Group and Subjects Not Meeting Inclusion Criteria

	SAI n=204 Frequency (%)	Usual Care n=220 Frequency (%)	Excluded n=547 Frequency (%)	Total n=971 Frequency (%)
HIV Disease Status				
HIV (non-AIDS)	87 (42.6)	68 (30.9)	172 (31.4)	327 (33.7)
AIDS	117 (57.4)	152 (69.1)	375 (68.6)	644 (66.3)
HIV Risk Factor				
MSM	85 (41.7)	61 (27.7)	152 (27.8)	298 (30.7)
Heterosexual	106 (52.0)	127 (57.7)	319 (58.3)	552 (56.8)
IDU	10 (4.9)	26 (11.8)	63 (11.5)	99 (10.2)
Other	3 (1.5)	6 (2.7)	13 (2.4)	22 (2.3)
Presence of Active Substance Abuse				
Yes	18 (8.8)	25 (11.4)	67 (12.2)	110 (11.3)
No	186 (91.2)	195 (88.6)	480 (87.8)	861 (88.7)
Presence of Active MH Disorder				
Yes	54 (26.5)	65 (29.5)	162 (29.6)	281 (28.9)
No	150 (73.5)	155 (70.5)	385 (70.4)	690 (71.1)

In summary, the sociodemographic, HIV disease, and comorbid characteristics between the usual care group and the group excluded from the study were approximately

equivalent. Chi-square tests were performed to look for significant differences in characteristics between these groups. No significant differences were found.

Characteristics of the Study Sample

The mean age of the sample was 44.3 years with a range of 19-76 years (*SD*: 9.36 years). The majority of subjects in the sample were men (n=299; 70.5%) and self-identified as non-Hispanic (n=309, 72.9%). The majority of the subjects were white (n=229, 54%) and 186 (43.9%) were black. The primary risk factors associated with HIV infection for the sample were (a) heterosexual (n=233, 55%); (b) men having sex with men (n=146, 34.4%); and (c) injection drug use (n=36, 8.5%). The mean time living with HIV disease was 7.6 years with a range of 1-25 years. The most common ARV regimen in the sample was protease inhibitor based (n=235; 55.4%). Subjects had a daily pill burden range from 2 to 15 pills per day with a mean daily pill burden of 5.

The SAI group included higher percentages of both younger patients (19-29 years) and patients in the 50-59 year age range. These differences were significant (Chi-square 15.897, *df* 4, p=.003). A higher percentage of white patients were seen in the SAI group while the usual care group included a higher percentage of black subjects. These differences were significant (Chi square 6.994; *df* 2, p=.03). Table 15 displays the frequency and percent for the demographic factors (gender, race, ethnicity, and age) of the patients who met inclusion criteria.

Table 15

Sociodemographic Composition of the Study Groups

Characteristics	SAI $n = 204$ Frequency (percent)	Usual Care $n = 220$ Frequency (percent)	Total $N = 424$ Frequency (percent)
Gender			
Male	152 (74.5)	147 (66.8)	299 (70.5)
Female	52 (25.5)	73 (33.2)	125 (29.5)
Race *			
White	123 (60.3)	106 (48.2)	229 (54.0)
Black	76 (37.3)	110 (50.0)	186 (43.9)
Other	5 (2.5)	4 (1.8)	9 (2.1)
Ethnicity			
Non-Hispanic	144 (70.6)	165 (75)	309 (72.9)
Hispanic	60 (29.4)	55 (25)	115 (27.1)
Age at time of study (years)**			
19-29	22 (10.8)	9 (4.1)	31 (7.3)
30-39	52 (25.5)	42 (19.1)	94 (22.2)
40-49	79 (38.7)	99 (45.0)	179 (42.0)
50-59	46 (22.5)	52 (3.6)	98 (23.1)
> 60	5 (2.5)	18 (8.2)	23 (5.4)

*Note.**=p<.05; **=p<.01

Preliminary analyses demonstrated that several covariates had small cell sizes. Consequently several covariates were collapsed into fewer categories to provide the reader with more useful information related to the population. Age of the participants was collapsed from a continuous variable to an ordinal variable with 5 age groups. Income levels were reduced from four groups to three due to small sample size in the upper income range. Three male transgender patients were grouped as male. Several HIV risk factors were grouped as "other" due to small cell sizes. Finally, the number of years living with HIV disease was collapsed into four groups.

Health and Income Related Characteristics

Table 16 displays the frequency for housing factors, health insurance, income, and HIV disease specific information. As expected, a higher percentage of subjects in the usual care group had health insurance while subjects in the SAI relied on the ADAP to fund their medication. These differences were significant (Chi-Square 109.849, *df* 1, p<.0005). More subjects in the usual care group had lower income (<100 FPL) while a higher percentage of subjects in the SAI had higher income (>200% FPL). These differences were also significant (Chi-Square 18.5, *df* 2, p<.0005). There was a higher percentage of subjects with a risk factor of MSM in the SAI and a higher percentage of IDUs in the usual care group (Chi-square 13.364, *df* 3, p=.004). Lastly, there was a higher percentage of patients with an AIDS diagnosis in the usual care group (Chi-Square 6.288, *df* 1, p=.012).

Substance Abuse and Mental Health Disorders

Table 17 displays the frequency and percentage of patients diagnosed as having an active substance abuse problem or a mental health disorder (depression, bipolar disorder, or anxiety). The SAI group and usual care group were approximately equivalent. A total of 43 patients (10.1%) were identified as having an active substance abuse problem while 119 (28.1%) were diagnosed as having mental health disorder.

Table 16

Health and Income Related Characteristics of the Study Group

Characteristics	SAI *n* = 204 Frequency (percent)	Usual Care *n* = 220 Frequency (percent)	Total *N* = 424 Frequency (percent)
Housing Status			
Permanent	201 (98.5)	215 (97.7)	416 (98.1)
Nonpermanent	3 (1.5)	5 (2.3)	8 (1.9)
HIV Risk Factor**			
MSM	85 (41.6)	61 (27.8)	146 (34.4)
Heterosexual	106 (52.0)	127 (57.7)	233 (55.0)
IDU	10 (4.9)	26 (11.8)	36 (8.5)
Other	3 (1.5)	6 (2.7)	9 (2.1)
Years Living with HIV			
≤5	88 (43.1)	89 (40.5)	177 (42.7)
6-10	55 (27.0)	73 (33.2)	128 (30.2)
11-15	36 (17.6)	41 (18.6)	77 (18.2)
>15	25 (12.3)	17 (7.7)	42 (9.9)
Income Level *** (% Federal Poverty Level)			
<100 %	124 (60.8)	168 (76.3)	292 (68.9)
101-200 %	55 (27.0)	46 (21.0)	101 (23.8)
> 200 %	25 (12.2)	6 (2.7)	31 (7.3)
Health Insurance***			
Yes	69 (33.8)	219 (99.5)	288 (67.9)
No	135 (66.2)	1 (0.5)	136 (32.1)
HIV Disease Status*			
HIV (non-AIDS)	87 (42.6)	68 (30.9)	155 (36.6)
AIDS	117 (57.4)	152 (69.1)	269 (63.4)

*Note.**=p<.05; **=p<.01; ***p<.001

Table 17

Substance Abuse and Mental Health Disorders in Study Group

Characteristics	SAI *n* = 204 Frequency (percent)	Usual Care *n* = 220 Frequency (percent)	Total *N* = 424 Frequency (percent)
History of Active Substance Abuse			
Yes	18 (8.8)	25 (11.4)	43 (10.1)
No	186 (91.2)	195 (88.6)	381 (89.9)
Presence of Mental Health Disorder			
Yes	54 (26.5)	65 (29.5)	119 (28.1)
No	150 (73.5)	155 (70.5)	305 (71.9)

ARV Therapy Characteristics

Table 18 describes the use of antiretroviral therapy associated with the study population. There was a significant difference between the groups related to the type of ARV regimen subjects received (Chi-Square: 7.672, *df* 2, p=.022). More than half of the patients in each group received a protease inhibitor-based regimen. Approximately 6% of all patients received a non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen during the study period with a higher percentage in the SAI group. Based on the DHHS guidelines in place during 2005, triple-NRTI regimens were not recommended regimens (National Institutes of Health, 2006).

The mean daily pill burden was 5.4 pills per day with a range of 2-15 pills per day. Over two-thirds of all patients received a regimen that required twice-daily dosing.

Table 18

Use of Antiretroviral Medications in Study Groups

Characteristics	SAI *n* = 204 Frequency (percent)	Usual Care *n* = 220 Frequency (percent)	Total *N* = 424 Frequency (percent)
Type of Regimen*			
Protease Inhibitor	112 (54.9)	123 (55.9)	235 (55.4)
NNRTI	74 (36.3)	91 (41.4)	165 (38.9)
Triple NRTI	18 (8.8)	6 (2.7)	24 (5.7)
Dosing Frequency			
Once Daily	59 (28.9)	73 (33.2)	132 (31.1)
Twice Daily	145 (71.1)	147 (66.8)	292 (68.9)
Daily ARV Pill Burden			
2-4	89 (43.6)	84 (38.2)	173 (40.8)
5-8	99 (48.5)	105 (47.7)	204 (48.1)
9-15	16 (7.8)	31 (14.1)	47 (11.1)

*Note.**=p<.05

Adherence Services and Intervention

The majority of the study population (92.7%) did not receive adherence counseling or intervention (n=393). A total of 31 patients (7.3%) received at least one face-to-face counseling session with the adherence specialist. Subjects received anywhere from one session to 23 sessions with a range of total counseling time from 30 minutes to 1,230 minutes. One outlier received 23 sessions with a cumulative counseling time of 1,230 minutes. With this outlier removed from analysis, the range of counseling time was 30-360 minutes with a mean of 91 minutes. Fewer than 4% of all patients received adherence aids such as pill boxes, customized medication schedules, and alarm watches (n=16). There were no significant differences related to adherence services and

interventions between the SAI and usual care group. Table 19 displays the frequency and percentages of adherence counseling services and interventions received by subjects.

Table 19

Adherence Services and Intervention

Adherence Measures	SAI *n* = 204 Frequency (percent)	Usual Care *n* = 220 Frequency (percent)	Total *N* = 424 Frequency (percent)
Received Adherence Counseling Session			
Yes	16 (7.8)	15 (6.8)	31 7.3
No	188 (92.2)	205 (93.2)	393 92.7
Adherence Counseling: (Minutes)			
0	188 (92.2)	205 (93.2)	393 (92.7)
30-60	5 (2.5)	3 (1.4)	8 (1.9)
61-120	9 (4.4)	7 (3.2)	16 (3.8)
>120	2 (1.0)	5 (2.3)	7 (1.7)
Number of Face-to-Face Adherence Counseling Sessions (per patient)			
0	188 (92.2)	205 (93.2)	393 (92.7)
1	12 (5.9)	11 (5.0)	23 (5.4)
2	3 (1.5)	1 (0.5)	4 (0.9)
3	1 (0.5)	1 (0.5)	2 (0.5)
5	0 0	1 (0.5)	1 (0.2)
>5	0 0	1 (0.5)	1 (0.2)
Adherence Aids Prescribed			
Yes	6 (2.9)	10 (4.5)	16 (3.8)
No	198 (97.1)	210 (95.5)	408 (96.2)

Self-Reported and Pharmacy Refill Adherence

Characteristics related to self-reported adherence and pharmacy refill adherence are summarized in Table 20. Three hundred sixty-four patients (85.8%) self-reported medication adherence of at least 90% while 60 patients (14.2%) reported adherence rates less than 90%. A higher percentage of subjects self-reported adherence rates ≥ 90% in the SAI group. There were significant differences between the two groups (Chi-square:19.581, *df* 1, p<.0005).

Overall, adherence levels of at least 90% as measured by pharmacy refill pick-up were lower than the self-report measurements. A greater percentage of patients in the SAI group had pharmacy refill adherence rates ≥ 90%. These differences were significant (Chi-Square: 7.578, *df* 1, p=.006).

Table 20

Self-Reported Adherence and Pharmacy Refill Adherence

Adherence Measures	SAI Frequency (percent) *n* = 204	Usual Care Frequency (percent) *n* = 220	Total Frequency (percent) *N* = 424
Self-Report Adherence***			
≥ 90%	191 (93.6)	173 (78.6)	364 (85.8)
< 90%	13 (6.4)	47 (21.4)	60 (14.2)
Pharmacy Refill Adherence**			
≥ 90%	120 (58.8)	100 (45.5)	220 (51.9)
< 90%	84 (41.2)	120 (54.5)	204 (48.1)

Note. **=p< .01; ***p<.001

Treatment Response

The majority of subjects demonstrated a favorable (stable or increasing) CD4 lymphocyte response (63.9%). A higher percentage of these subjects were seen in the SAI group but this was not a statistically significant finding. However, a significantly higher percentage of patients in the SAI (79.4%) demonstrated a favorable virologic response (stable or declining HIV RNA level) compared with 45.9% in the usual care group (Chi-square 50.442, df 1, p<.0005). Table 21 depicts this information.

Table 21

Treatment Response by Group Membership

Adherence Measures	SAI Frequency (percent) *n* = 204	Usual Care Frequency (percent) *n* = 220	Total Frequency (percent) *N* = 424
CD4 Lymphocyte Count			
Stable or Increasing	139 (68.1)	132 (60.0)	271 (63.9)
Decreasing	65 (31.9)	88 (40.0)	153 (36.1)
HIV RNA Response***			
Stable or Declining	162 (79.4)	101 (45.9)	263 (62.0)
Increasing	42 (20.6)	119 (54.1)	161 (38.0)

Note. ***p<.001

Summary

Bivariate and descriptive analyses related to the study groups and covariates have been presented. Several statistically significant differences between the SAI and usual care group have been reported.

Bivariate Analyses and Logistic Regression

The following section will describe the bivariate analyses and logistic regression associated with the study. Initially a series of Chi-Square analyses were conducted to investigate the relationship between adherence outcomes (self-reported and pharmacy refill), treatment response (CD4 lymphocyte and HIV RNA), treatment conditions (SAI and usual care) and the covariates in the study. Variables found to be independently associated with adherence or treatment response at a significance level of $p = .10$ or less were considered for inclusion in a regression model.

Logistic regression was performed on each outcome variable (self-reported adherence, pharmacy refill adherence, CD4 lymphocyte response and HIV RNA response) to test the effects of the treatment condition while controlling for potentially confounding effects (adherence services and intervention, HIV disease specific factors, ARV specific factors and sociodemographic factors).

All models were checked for high intercorrelation using collinearity diagnostics within SPSS. Tolerance values were satisfactory with no evidence of intercorrelation between covariates. Singularity was assessed using SPSS. Variance inflation factor values were all greater than 10 suggesting no evidence of singularity. Omnibus tests of model coefficients were performed on each of the models and values $<.05$ were obtained. These findings suggest acceptable goodness of fit for the models. Hosmer and Lemeshow tests were performed for each of the models and values $>.05$ were calculated. These findings also suggest support of the models.

Study Aim One: Adherence Outcomes

The purpose of the first study aim was to determine whether patients participating in the SAI program experienced higher levels of adherence compared to patients receiving usual care, controlling for adherence services and intervention, HIV disease-specific factors, ARV-specific factors, and sociodemographic factors. Two hypotheses were tested:

1) Patients participating in the SAI program will have higher levels of self-reported adherence compared to patients receiving usual care, controlling for selected covariates.
2) Patients participating in the SAI program will have higher levels of pharmacy refill adherence compared to patients receiving usual care, controlling for selected covariates.

Self-Reported Adherence

Bivariate analyses were calculated on self-reported adherence and each of the covariates and the treatment condition. The data are displayed in Tables 22 and 23. There were several significant findings. Approximately 65% of patients who had health insurance self-reported adherence rates of at least 90% while a higher percentage (81.7%) of subjects without insurance self-reported adherence levels $\geq$ 90%. Individuals who reported acquisition of HIV infection associated with intravenous drug use (IDU) route had lower self-reported medication adherence while the men who have sex with men (MSM) group reported higher levels. A higher percentage of subjects that did not have a history of active substance abuse (91.2%) self-reported adherence levels $\geq$ 90% compared

to those with active substance abuse (81.7%). Finally, subjects with a history of mental health disorders self-reported a higher percentage of medication adherence below the acceptable rate of 90%. Lastly, subjects participating in the SAI were more likely to report adherence levels ≥ 90%.

Table 22

Bivariate Analysis - Self-Reported Adherence: Sociodemographic and HIV Disease Specific Factors

Covariates	Self-Reported Adherence ≥ 90%		Self-Reported Adherence < 90%		Pearson Chi-Square (significance level .10 or less)
	n	(%)	n	(%)	
Sociodemographic Covariates					
Age (years)					
19-29	28	(7.7)	3	(5.0)	
30-39	83	(22.8)	11	(18.3)	
40-49	149	(40.9)	29	(48.3)	
50-59	86	(23.6)	12	(20)	
> 60	18	(4.9)	5	(8.3)	
Gender					
Male	259	(71.2)	40	(66.7)	
Female	105	(28.8)	20	(33.3)	
Race					
White	199	(54.7)	30	(50.0)	
Black	159	(43.7)	27	(45.0)	
Other	6	(1.6)	3	(5.0)	
Ethnicity					
Non-Hispanic	268	(73.6)	41	(68.3)	
Hispanic	96	(26.4)	19	(31.7)	
Income (% Federal Poverty Level)					
<100 %	244	(67.0)	48	(80.0)	
101-200 %	90	(24.7)	41	(18.3)	
> 200 %	30	(8.2)	1	(1.7)	
Housing Status					
Permanent	359	(98.6)	57	(95.0)	
Nonpermanent	5	(1.4)	3	(5.0)	
Health Insurance					
Yes	239	(65.7)	49	(81.7)	6.059, *df* 1, p=.014
No	125	(34.3)	11	(18.3)	

Table 22 continued

Bivariate Analysis - Self-Reported Adherence: Sociodemographic and HIV Disease Specific Factors

Covariates	Self-Reported Adherence ≥ 90% n	(%)	< 90% n	(%)	Pearson Chi-Square (significance level .10 or less)
HIV Disease Specific Covariates					
HIV Risk Factor					
MSM	132	(36.3)	14	(23.3)	
Heterosexual	197	(54.1)	36	(60.0)	9.811, *df* 3, p=.020
IDU	26	(7.1)	10	(16.7)	
Other	9	(2.5)	0	(0)	
Disease Stage					
HIV (non-AIDS)	138	(37.9)	17	(28.3)	
AIDS	226	(62.1)	43	(71.7)	
Years Living with HIV					
≤5	149	(40.9)	28	(46.7)	
6-10	109	(29.9)	19	(31.7)	
11-15	69	(19.0)	8	(13.3)	
>15	37	(10.2)	5	(8.3)	
Active Substance Abuse					
Yes	32	(8.8)	11	(18.3)	5.147, *df* 1, p=.023
No	332	(91.2)	49	(81.7)	
Mental Health Disorder					
Yes	96	(26.4)	23	(38.3)	3.649, *df* 1, p=.056
No	268	(73.6)	37	(61.7)	

Table 23

Bivariate Analysis- Self-Reported Adherence: ARV and Adherence Counseling and Intervention Specific Factors

Covariates	Self-Reported Adherence				Pearson Chi-Square (significance level .10 or less)
	≥ 90%		< 90%		
	n	(%)	n	(%)	
ARV Specific Covariates					
Dosing Frequency					
Once Daily	113	(31.0)	19	(31.7)	
Twice Daily	251	(69.0)	41	(68.3)	
Type of ARV Regimen					
Protease Inhibitor	199	(54.7)	36	(60.0)	
NNRTI	145	(39.8)	20	(33.3)	
Triple NRTI	20	(5.5)	4	(6.7)	
Daily ARV Pill Burden					
2-4	151	(41.5)	22	(36.7)	
5-8	174	(47.8)	30	(50.0)	
9-15	39	(10.7)	8	(13.3)	
Adherence Counseling and Intervention					
Received Adherence Counseling	24	(6.6)	7	(11.7)	
Yes	340	(93.4)	53	(88.3)	
No					
No. of Counseling Sessions					
0	340	(93.4)	53	(88.3)	
1	18	(4.9)	5	(8.3)	
2	2	(0.5)	2	(3.3)	
3	2	(0.5)	0	(0)	
4	1	(0.3)	0	(0)	
>5	1	(0.3)	0	(0)	
Adherence Counseling (minutes)					
0	340	(96.4)	53	(88.3)	
30-60	7	(1.9)	1	(1.7)	
61-120	13	(3.6)	3	(5.0)	
>120	4	(1.1)	3	(5.0)	
Adherence Aids Prescribed					
Yes	13	(3.6)	3	(5.0)	
No	351	(96.4)	57	(95.0)	
Treatment Condition					
SAI	191	(52.5)	13	(21.7)	19.581, *df* 1, p<.0005
Usual Care	173	(47.45)	47	(78.3)	

The initial factors included in the logistic regression included income, housing status, health insurance, HIV risk factor, active substance abuse, mental health disorder and treatment condition. Through an iterative process factors that did not make significant contributions in the regression were removed and regression was repeated with the remaining factors. Factors were reinserted if the model was negatively affected by the removal of a covariate. Covariates selectively removed from the regression included income, health insurance, HIV risk factor, and mental health disorder. Housing status was removed because a small sample size related to nonpermanently housed subjects created unstable results.

After adjusting for covariates, subjects in the SAI group remained significantly more likely to self-report medication adherence $\geq$ 90% as compared to the usual care group (adjusted OR = 3.944; 95% CI 2.058, 7.557; $p < 0.0005$). Additionally, patients with a history of substance abuse were less likely to report favorable medication adherence (OR 2.237; CI 1.033, 4.864; p=.041). Approximately 68% of all cases were explained by this regression model (c-statistic 0.677). Based on the logistic regression results, the null hypothesis of no difference in self-reported adherence between the two groups was rejected. Patients who participated in the SAI program were almost four times more likely to report adherence levels $\geq$ 90%. These results are presented in Table 24.

Table 24

Logistic Regression Analysis: Summary of Predictors of Self-Reported Adherence (≥ 90%)

Variable	β	Odds Ratio	95% Confidence Interval	Wald Chi-Square	P
Treatment Condition	1.372	3.944	2.058, 7.557	17.017	<.0005
History of Substance Use	-0.805	2.237	1.033, 4.864	4.167	0.041

Note. Overall model, Chi-Square = 24.566, *df*=2, *p <.0005*.

Pharmacy Refill Adherence

Bivariate analyses were calculated on pharmacy refill adherence and each of the covariates and the treatment condition. The data are displayed in Table 25. There were several significant findings. In most of the age groups, similar percentages of subjects had both favorable (≥ 90%) and unfavorable (<90%) pharmacy refill adherence. However, nearly twice as many subjects in the age range of 30-39 years had unfavorable pharmacy refill adherence (29.4%) while only 15.5% of subjects had favorable adherence. An inverse relationship was seen in the age group of 50-59 years: nearly double the percentage of subjects demonstrated favorable adherence (29.1%) while 16.7% had unfavorable levels. These differences were significant (Chi-Square 17.287, *df* 4, p=.002). White patients also had a higher percentage of favorable pharmacy refill adherence.

A higher percentage of subjects with household income <100% of Federal Poverty Level demonstrated lower adherence levels (76% compared with 62.3%) while those with income levels between 101-200% had nearly twice the rate of favorable pharmacy refill adherence at a level ≥ 90% (29.5% compared to 17.6%). A greater percentage of subjects without health insurance (38.2%) demonstrated pharmacy refill

adherence ≥ 90% compared with insured patients (25.5%) (Chi-Square 7.862, *df* 1, p=.005). Of subjects reporting active substance use, almost twice as many demonstrated pharmacy refill adherence <90% (13.2%) compared to those with favorable refill adherence (7.3%).

Table 25

Bivariate Analysis- Pharmacy Refill Adherence: Sociodemographic and HIV Disease Specific Factors

Covariates	Pharmacy Refill Adherence ≥ 90% n=204		< 90% n=220		Pearson Chi-Square (significance level .10 or less)
	n	(%)	n	(%)	
Sociodemographic Covariates					
Age (years)					
18-29	14	(6.4)	17	(8.3)	
30-39	34	(15.5)	60	(29.4)	
40-49	95	(43.2)	83	(40.7)	17.287, *df* 4, p=.002
50-59	64	(29.1)	34	(16.7)	
> 60	13	(5.9)	10	(4.9)	
Gender					
Male	160	(72.7)	139	(68.1)	
Female	60	(27.3)	65	(31.9)	
Race					
White	137	(62.3)	92	(45.1)	
Black	77	(35.0)	109	(53.4)	14.765, *df* 2, p=.001
Other	6	(2.7)	3	(1.5)	
Ethnicity					
Non-Hispanic	155	(70.5)	154	(75.5)	
Hispanic	65	(29.5)	50	(24.5)	
Income (% Federal Poverty Level)					
<100 %	137	(62.3)	155	(76.0)	
101-200 %	65	(29.5)	36	(17.6)	9.653, *df* 2, p=.008
> 200 %	18	(8.2)	13	(6.4)	
Housing Status					
Permanent	215	(97.7)	201	(98.5)	
Nonpermanent	5	(2.3)	3	(1.5)	
Health Insurance					
Yes	136	(61.8)	152	(74.5)	7.862, *df* 1, p=.005
No	84	(38.2)	52	(25.5)	

Table 25 continued

Bivariate Analysis- Pharmacy Refill Adherence: Sociodemographic and HIV Disease Specific Factors

Covariates	Pharmacy Refill Adherence ≥ 90% n=204 n (%)		< 90% n=220 n (%)		Pearson Chi-Square (significance level .10 or less)
HIV Disease Specific Factors covariates					
HIV Risk Factor					
MSM	88	(40.0)	58	(28.4)	
Heterosexual	111	(50.5)	122	(59.8)	7.09, *df* 3, p=.069
IDU	18	(8.2)	18	(8.8)	
Other	3	(1.4)	6	(2.9)	
Disease Stage					
HIV (non-AIDS)	90	(40.9)	65	(31.9)	3.735, *df* 1, p=.053
AIDS	130	(50.1)	139	(68.1)	
Years Living with HIV					
≤5	96	(43.6)	81	(39.7)	
6-10	73	(33.2)	55	(27.0)	
11-15	32	(14.5)	45	(21.1)	
>15	19	(8.6)	23	(11.3)	
Active Substance Abuse					
Yes	16	(7.3)	27	(13.2)	4.129, *df* 1, p=.042
No	204	(92.7)	177	(86.8)	
Mental Health Disorder					
Yes	63	(52.9)	56	(47.1)	
No	157	(51.5)	148	(48.5)	

There were no significant differences between pharmacy refill adherence and ARV characteristics and adherence counseling and intervention specific factors. Lastly, a higher percentage (54.5%) of subjects participating in the SAI had pharmacy refill adherence ≥ 90% compared to those receiving usual care (45.5%) (Chi-square 0.578, *df* 1, p=.008). These data are displayed in Table 26.

The initial factors included in the logistic regression for pharmacy refill adherence included age, race, income, health insurance, HIV risk factor, disease stage, active substance abuse, time associated with adherence counseling and treatment condition. Factors that did not have significant contributions in the regression were removed including time associated with adherence counseling, and active substance abuse. Health

insurance was removed as it was believed that this factor and the treatment condition of SAI explained the same information.

Table 26

Bivariate Analysis - Pharmacy Refill Adherence: ARV and Adherence Counseling and Intervention Specific Factors

Covariates	Pharmacy Refill Adherence ≥ 90% n	(%)	< 90% n	(%)	Pearson Chi-Square (significance level .10 or less)
ARV Covariates					
Dosing Frequency	65	(29.5)	67	(32.8)	
Once Daily	155	(70.5)	137	(67.2)	
Twice Daily					
Type of ARV Regimen					
Protease Inhibitor	115	(52.3)	120	(58.8)	
NNRTI	92	(41.8)	73	(35.8)	
Triple NRTI	13	(5.9)	11	(5.4)	
Daily ARV Pill Burden					
2-4	95	(43.2)	78	(38.2)	
5-8	104	(47.3)	100	(49.0)	
9-15	21	(9.5)	26	(12.7)	
Adherence Services and Intervention					
Received Adherence Counseling					
Yes	12	(5.5)	19	(9.3)	
No	208	(94.5)	185	(90.7)	
No. of Counseling Sessions					
0	208	(94.5)	185	(90.7)	
1	10	(4.5)	13	(6.4)	
2	2	(0.9)	2	(1.0)	
3	0	(0)	2	(1.0)	
4	0	(0)	1	(0.5)	
>5	0	(0)	1	(0.5)	
Adherence Counseling (minutes)					
0	208	(94.5)	185	(90.7)	
30-60	2	(0.9)	6	(2.9)	
61-120	9	(4.1)	7	(3.4)	
>120	1	(0.5)	6	(2.9)	
Adherence Aids Prescribed					
Yes	6	(2.7)	10	(4.9)	
No	214	(97.3)	194	(95.1)	
Treatment Condition					
SAI	120	(54.5)	84	(41.2)	7.578, *df* 1, p=.006
Usual Care	100	(45.5)	120	(58.8)	

After adjusting for covariates, subjects in the SAI group remained significantly more likely to achieve 90% or more pharmacy refill adherence compared to the usual care group (OR 1.833, CI 1.206, 2.788; p=.005). In this regression, age was treated as a continuous variable. For every increase in year of age, there was approximately a 5% increase in the likelihood of having a favorable pharmacy refill adherence outcome. White race had a negative association with pharmacy refill adherence (OR 0.496; CI .039, 0.749; p=.001). Approximately 68% of all cases were correctly predicted by this regression model (c-statistic 0.683). Based on the logistic regression results, the null hypothesis for hypothesis number two was rejected. These results are presented in Table 27.

Table 27

Logistic Regression Analysis: Summary of Predictors of Pharmacy Refill Adherence

Variable	β	Odds Ratio	95% Confidence Interval	Wald Chi-Square	P
Treatment Condition	0.606	1.833	1.206 – 2.788	8.038	0.005
Age	0.049	1.050	1.026 – 1.074	17.633	<.0005
Race	-0.701	0.496	0.329 – 0.749	11.150	0.001

Note. Overall model, Chi-Square = 43.012, *df*=5, $p < .0005$.

Study Aim One: Summary

The two hypotheses associated with the first study aim were supported. Logistic regression analyses support significant differences in self-reported adherence and pharmacy refill adherence associated with participation in the SAI program.

Study Aim Two: Treatment Response Outcomes

The purpose of the second study aim was to determine whether patients participating in the SAI program experience improved response to treatment compared to patients receiving usual care, controlling for HIV disease-specific factors, ARV-specific factors, and sociodemographic factors. Two hypotheses were tested:

1) Patients participating in the SAI program will have better immunologic (CD4 lymphocyte) responses to HAART compared to patients receiving usual care, controlling for selected covariates.
2) Patients participating in the SAI program will have better virologic (HIV RNA) responses compared to patients receiving usual care, controlling for selected covariates.

CD4 Lymphocyte Response

There were few statistically significant findings in the bivariate analyses of CD4 lymphocyte response and each of the covariates and the treatment condition. Overall, approximately 64% of subjects in this study demonstrated an unfavorable declining CD4 lymphocyte response. Although the difference is not significant, a larger percentage of subjects identifying as Hispanic had a declining CD4 response (57.4% compared with 33.7% for non-Hispanic) (Chi-square 2.912, *df* 1, p=.088). All 8 of the subjects with non-permanent housing demonstrated a stable or increasing CD4 response (Chi square 3.147, *df* 1, p=.076, Yates' Correction for Continuity). This information is displayed in Table 28.

Table 28

Bivariate Analysis - CD4 Lymphocyte Response: Sociodemographic and HIV Disease Specific Factors

Covariates	CD4 Lymphocyte Declining N	(%)	Stable/Increasing n	(%)	Pearson Chi-Square (significance level .10 or less)
Sociodemographic Covariates					
Age (years)					
19-29	13	(8.5)	18	(6.6)	
30-39	35	(22.9)	59	(21.8	
40-49	58	(37.9)	120	(44.3)	
50-59	36	(23.5)	62	(22.9)	
> 60	11	(7.2)	12	(4.4)	
Gender					
Male	112	(73.2)	187	(69.0)	
Female	41	(26.8)	84	(31.0)	
Race					
White	78	(51.0)	151	(55.7)	
Black	71	(46.4)	115	(42.4)	
Other	4	(2.6)	5	(1.8)	
Ethnicity					
Non-Hispanic	104	(68.0)	205	(75.6)	2.912, *df* 1 p=.088
Hispanic	49	(32.0)	66	(24.4)	
Income					
(% Federal Poverty Level)					
<100 %	113	(73.9)	179	(66.1)	
101-200 %	30	(19.6)	71	(26.2)	
> 200 %	10	(6.5)	21	(7.7)	
Housing Status		b		g	
Nonpermanent	0	(0)	8	(3.0)	3.147, *df* 1, p=.076
Permanent	153	(100)	263	(97.0)	(Yates' Correction for Continuity)
Health Insurance					
Yes	46	(30.1)	90	(33.2)	
No	107	(69.9)	180	(66.8)	
HIV Disease Specific Factors					
HIV Risk Factor					
MSM	52	(34.0)	94	(34.7)	
Heterosexual	82	(53.6)	151	(55.7)	
IDU	16	(10.5)	20	(7.4)	
Other	3	(2.0)	6	(2.2)	
Disease Stage					
HIV (non-AIDS)	59	(38.6)	96	(35.4)	
AIDS	94	(61.4)	175	(64.6)	
Years Living with HIV					
≤5	61	(39.9)	116	(42.8)	
6-10	43	(28.1)	85	(31.4)	
11-15	33	(21.6)	44	(16.2)	
>15	16	(10.5)	26	(9.6)	
Active Substance Abuse					
Yes	19	(12.4)	24	(8.9)	
No	134	(87.6)	247	(91.9)	
Mental Health Disorder					
Yes	46	(30.1)	73	(26.9)	
No	107	(69.9)	198	(73.1)	

Of the 271 subjects with a favorable CD4 response, 34.3% received a once daily regimen while 65.7% received a twice daily regimen (Chi-square 3.554, *df* 1, p=.059). Immunologic response based on pill burden was similar when subjects received 2-4 or 5-8 pills per day. However, when daily pill burden exceeded 8 pills per day, there were a higher percentage of subjects that had CD4 decline (Chi-square 8.719, *df* 2, p=.013). Lastly, 68% of subjects in the SAI (n=139) had a favorable immunologic response compared with only 60% of those in usual care (n=132) (Chi-square 3.039 *df* 1, p=.0816). Table 29 depicts this information.

Table 29

Bivariate Analysis- CD4 Lymphocyte Response: ARV and Adherence Counseling and Intervention Specific Factors

Covariates	CD4 Lymphocyte Declining n	(%)	Stable/Increasing n	(%)	Pearson Chi-Square (significance level .10 or less)
ARV Specific Covariates					
Dosing Frequency					
Once Daily	39	(25.5)	93	(34.3)	3.554, *df* 1, p=.059
Twice Daily	114	(74.5)	178	(65.7)	
Type of ARV Regimen					
Protease Inhibitor	89	(58.2)	146	(53.0)	
NNRTI	56	(36.6)	109	(40.2)	
Triple NRTI	8	(5.2)	16	(5.9)	
Daily ARV Pill Burden					
2-4	56	(36.6)	117	(43.2)	
5-8	71	(46.4)	133	(49.1)	8.719, *df* 2, p=.013
9-15	26	(17.0)	21	(7.7)	

Table 29 continued

Bivariate Analysis- CD4 Lymphocyte Response: ARV and Adherence Counseling and Intervention Specific Factors

Covariates	CD4 Lymphocyte Declining n	(%)	Stable/Increasing n	(%)	Pearson Chi-Square (significance level .10 or less)
Adherence Services and Intervention					
Received Adherence Counseling					
Yes	10	(6.5)	21	(7.7)	
No	143	(93.5)	250	(92.3)	
No. of Counseling Sessions					
0	143	(93.5)	250	(92.3)	
1	10	(6.5)	13	(4.8)	
2	0	(0)	4	(150)	
3	0	(0)	2	(0.7)	
4	0	(0)	1	(0.6)	
>5	0	(0)	1	(0.6)	
Adherence Counseling (minutes)					
0	143	(93.5)	250	(92.3)	
30-60	5	(3.3)	3	(1.1)	
61-120	4	(2.6)	12	(4.4)	
>120	1	(0.7)	6	(2.2)	
Adherence Aids Prescribed					
Yes	3	(2.0)	13	(4.8)	
No	150	(98.0)	258	(95.2)	
Treatment Condition					
SAI	65	(42.5)	139	(51.3)	3.039 *df* 1, p=.0816
Usual Care	88	(57.5)	132	(48.7)	

The initial factors included in the regression for CD4 lymphocyte response included ethnicity, housing status, ARV dosing, ARV daily pill burden, and treatment condition. Factors that did not have significant contributions in the regression were removed (housing status and ARV dosing) and regression was repeated with the remaining factors. The only significant finding in this regression was related to daily pill burden. Subjects receiving 2-4 tablets per day were less likely to achieve a favorable CD4 lymphocyte response (OR 0.917; CI 0.844, 0.996; p=.039). Approximately 59% of all cases were correctly predicted by this regression model (c-statistic 0.594). Based on

logistic regression analysis, the null hypothesis for the third research question was supported as no significant relationship was identified between the SAI program and CD4 lymphocyte response. These results are presented in Table 30.

Table 30

Logistic Regression Analysis: Summary of Predictors of CD4 Lymphocyte Response

Variable	β	Odds Ratio	95% Confidence Interval	Wald Chi-Square	P
Ethnicity	0.392	1.480	0.949 – 2.306	2.996	0.083
Daily Pill Burden	-.087	0.917	0.844 – 0.996	4.287	0.039
Treatment Condition	0.338	1.402	0.935 – 2.102	2.670	0.102

Note. Overall model, Chi-Square = 10.535, df=3, $p = .015$.

HIV RNA Response

There were a number of statistically significant findings in the bivariate analyses of HIV RNA response, the covariates and the treatment condition. The sociodemographic and HIV disease specific data are displayed in Table 31.

Table 31

Bivariate Analysis- HIV RNA Response: Sociodemographic and HIV Disease Specific Factors

Covariates	HIV RNA Response				Pearson Chi-Square (significance level .10 or less)
	Increasing		Stable/Decreasing		
	n	(%)	n	(%)	
Sociodemographic Covariates					
Age (years)					
19-29	9	(5.6)	22	(8.4)	
30-39	32	(19.9)	62	(23.6	
40-49	74	(46.0)	104	(39.5)	
50-59	34	(21.1)	64	(24.3)	
> 60	12	(7.5)	11	(4.2)	
Gender					
Male	113	(70.2)	186	(70.7)	
Female	48	(29.8)	77	(29.3)	
Race					
White	74	(46.0)	155	(58.9)	
Black	83	(51.6)	103	(39.2)	6.766, *df* 2, p=.034
Other	4	(2.5)	5	(1.9)	
Ethnicity					
Non-Hispanic	122	(75.8)	187	(71.1)	
Hispanic	39	(24.2)	76	(28.9)	
Income					
(% Federal Poverty					
Level)	117	(72.7)	175	(66.5)	5.112, *df* 2, p=.078
<100 %	28	(23.6)	63	(24.0)	
101-200 %	6	(3.7)	25	(9.5)	
> 200 %					
Housing Status					
Permanent	157	(97.5)	259	(98.5)	
Nonpermanent	4	(2.5)	4	(1.5)	
Health Insurance					
Yes	135	(83.9)	153	(58.2)	30.218, *df* 1 p<.0005
No	26	(16.1)	110	(41.8)	
HIV Disease Specific Covariates					
HIV Risk Factor					
MSM	53	(32.9)	93	(35.4	
Heterosexual	88	(54.7)	145	(55.1)	
IDU	15	(9.3)	21	(8.0)	
Other	5	(3.4)	4	(1.5)	
Disease Stage					
HIV (non-AIDS)	50	(31.1)	105	(39.9)	3.386, *df* 1, p=.066
AIDS	111	(68.9)	158	(60.1)	
Years Living with HIV					
≤5	62	(38.5)	115	(43.7)	
6-10	52	(32.3)	76	(28.9)	
11-15	32	(19.9)	45	(17.1)	
>15	15	(9.3)	27	(10.3	
Active Substance Abuse					
Yes	19	(11.8)	24	(9.1)	
No	142	(88.2)	239	(90.9)	
Mental Health Disorder					
Yes	47	(29.2)	72	(27.4)	
No	114	(70.8)	191	(72.6	

Bivariate analysis suggested there were racial differences related to virologic response. A higher percentage of white patients achieved or sustained a virologic response (58.9%) compared to blacks (39.2%) (Chi-square 6.766, *df* 2, p=.034). A higher percentage of subjects in the lowest income group experienced increasing HIV RNA while a greater percentage of patients at the highest income level of >200% FPL had a favorable virologic response (Chi-square 5.112, *df* 2, p=.078).

Sixty-two percent of all subjects had a favorable virologic response (n=263). Of these, 58.2% had insurance, 41.8% did not. Of the 161 subjects that had unfavorable virologic responses, 16.1% did not have insurance while 83.9% did have insurance (Chi square 30.218, *df* 1 p<.0005).

Almost two-thirds of the patients had a diagnosis of AIDS. Of patients with an unfavorable HIV RNA response, 68.9% had an AIDS diagnosis. Of the 163 subjects that had a favorable HIV RNA response, 60.1% had an AIDS diagnosis.

Although few patients received adherence aids (n=16), 87.5% of them were prescribed to subjects that demonstrated stable or declining HIV RNA (Chi-square 4.58, *df* 1, p=.032). Lastly, 61.6% of subjects participating in the SAI demonstrated favorable virologic responses compared to 38.4% of those in usual care (Chi-square 50.442, *df* 1, p<.0005). This data is presented in Table 32.

Table 32

Bivariate Analysis- HIV RNA Response: ARV and Adherence Counseling and Intervention Specific Factors

Covariates	CD4 Lymphocyte Declining n	(%)	Stable/Increasing n	(%))	Pearson Chi-Square (significance level .10 or less)
ARV Specific Covariates					
Dosing Frequency					
Once Daily	49	(30.4)	83	(31.6)	
Twice Daily	112	(69.6)	180	(68.4)	
Type of ARV Regimen					
Protease Inhibitor	89	(55.3)	146	(55.5)	
NNRTI	65	(40.4)	100	(38.0)	
Triple NRTI	7	(9.1)	17	(6.5)	
Daily ARV Pill Burden					
2-4	61	(37.9)	112	(42.6)	
5-8	76	(47.2)	128	(48.7)	
9-15	24	(14.9)	23	(8.7)	
Adherence Services and Intervention					
Received Adherence Counseling					
Yes	8	(5.0)	23	(8.7)	
No	153	(95.0)	240	(91.3)	
No. of Counseling Sessions					
0	153	(95.0)	240	(91.3)	
1	8	(5.0)	15	(5.7)	
2	0	(0)	4	(1.5)	
3	0	(0)	2	(0.8)	
4	0	(0)	1	(0.4)	
>5	0	(0)	1	(0.4)	
Adherence Counseling (minutes)					
0	153	(95.0)	240	(91.3)	
30-60	4	(2.5)	4	(1.5)	
61-120	4	(2.5)	12	(4.6)	
>120	0	(0)	7	(2.7)	
Adherence Aids Prescribed					
Yes	2	(1.2)	14	(5.3)	4.58, *df* 1, p=.032
No	159	(98.8)	249	(94.7)	
Treatment Condition					
SAI	42	(26.1)	162	(61.6)	50.442, *df* 1, p<.0005
Usual Care	119	(73.9)	101	(38.4)	

The initial factors included in the regression for HIV RNA response included race, income, health insurance, HIV disease stage, adherence aids prescribed and treatment condition. Factors that did not have significant contributions in the regression

were removed (race, health insurance and income) and regression was repeated with the remaining factors. After adjusting for covariates, subjects who participated in the SAI program were over four and a half times more likely to achieve a favorable virologic response (OR 4.573; CI 2.953, 7.080; p<.0005). Subjects who received an adherence aid were almost seven times more likely to achieve a favorable VL response (OR 6.87; CI 1.473, 32.072; p=.014). Approximately 73% of all cases were correctly predicted by this regression model (c-statistic 0.725). Based on this logistic regression, the null hypothesis of no differences in virologic response between the SAI and usual care group for hypothesis number four was rejected. These results are presented in Table 33.

Table 33

Logistic Regression Analysis: Summary of Predictors of HIV RNA Response

Variable	β	Odds Ratio	95% Confidence Interval	Wald Chi-Square	*p*
Treatment Condition	1.520	4.573	2.953 - 7.080	46.411	<.0005
Race	0.465	1.592	1.039 - 2.438	4.564	0.033
Adherence Aids	1.928	6.873	1.473 - 32.072	6.015	0.014

Note. Overall model, Chi-Square = 63.999, *df*=3, *p <.0005*.

Study Aim Two: Summary

The first hypothesis associated with study aim two was rejected as there were no significant differences in CD4 lymphocyte response between the SAI and usual care group. The second hypotheses was supported as logistic regression analyses

demonstrated significant differences in HIV RNA response associated with the SAI program.

Summary

This chapter has presented the statistical analyses for the investigation. Demographic results were presented first, followed by the results of bivariate analyses between the adherence outcomes, treatment outcomes, treatment groups and covariates. Finally, the results of the logistic regression for each study aim were presented. Three hypotheses were supported; one was rejected. In the concluding chapter, these results will be discussed along with a discussion of the implications for future research and nursing practice.

CHAPTER 5: DISCUSSSION, CONCLUSIONS AND RECOMMENDATIONS

Introduction

This final chapter presents a synthesis of the research results with a discussion of the findings, conclusions, study limitations and implications for clinical practice. Recommendations for dissemination of the findings and for future research are proposed.

Summary of the Study

The purpose of this retrospective comparative study was to better understand the effects of an existing antiretroviral access program on adherence to HAART and response to treatment compared to patients enrolled in usual care. In the structured adherence intervention (SAI) staff closely monitored monthly HIV medication refills and provided structured adherence interventions when indicated. Patients receiving usual care were enrolled in a Medicaid-funded medication access program and did not receive ongoing medication refill monitoring and structured adherence intervention. Both patient groups received their ARV medications and outpatient HIV medical care from a single treatment center and pharmacy.

The study included 424 subjects comparably distributed between the usual care and SAI group. Bivariate analyses were used to identify significant associations between the usual care and SAI group regarding sociodemographic characteristics, HIV disease related factors, ARV-related characteristics and utilization of adherence services and intervention. Logistic regression was performed to identify predictors of self-reported medication adherence, pharmacy refill adherence, CD4 lymphocyte response and HIV

RNA response. This research provided valuable information related to antiretroviral adherence and treatment outcomes for patients participating in usual care and a state-based antiretroviral access program. The study is unique in that no known investigations have previously tested a structured programmatic intervention on ARV adherence and HIV treatment outcomes.

Discussion and Conclusions

The following is a discussion of the findings according to the study aims and research questions in the study along with the conclusions that may be drawn from this research study.

Study Aim One

The first study aim was to determine whether patients participating in the SAI program experienced higher levels of adherence compared to patients receiving usual care, controlling for adherence services and intervention, HIV disease-specific factors, ARV-specific factors, and sociodemographic factors. To answer the first research question, "Is there a difference in self-reported adherence in subjects participating in the SAI program compared to those who receive usual care?," logistic regression was performed to test the null hypotheses that there were no differences between self-reported adherence between participants in the usual care group of subjects and the subjects participating in the SAI. After controlling for covariates, subjects in the SAI group were significantly more likely to self-report medication adherence $\geq$ 90% as compared to the usual care group (OR = 3.944; 95% CI 2.058, 7.557; $p < 0.0005$) and the null hypothesis was rejected.

To answer the second research question, "Is there a difference in pharmacy refill adherence in subjects participating in the SAI program compared to those who receive usual care?," logistic regression was performed to test the null hypothesis that there were no differences between pharmacy refill adherence between participants in the usual care group of subjects and the subjects participating in the SAI. After adjusting for covariates, subjects in the SAI group remained significantly more likely to achieve 90% or more pharmacy refill adherence compared to the usual care group (OR 1.833, 95% CI 1.206, 2.788; p=.005). The null hypothesis was rejected.

Several unexpected findings were seen in this study including low overall utilization of the adherence specialist and comparable use of the adherence specialist between the two study groups. The majority of the study population (92.7%) did not receive any adherence counseling or intervention (n=393) from the adherence specialist. A total of only 31 subjects (7.3%) received at least one face-to-face counseling session with the adherence specialist. The range of counseling time was 30-360 minutes with a mean of 91 minutes during the 6 month study period. Fewer than 4% of all patients received adherence aids such as pill boxes, customized medication schedules, and alarm watches (n=16) from the adherence specialist.

There are several potential explanations for the unexpected low utilization of the adherence specialist's services. Primary healthcare providers (PCPs) delivering outpatient care services to the subjects may have provided adherence interventions on their own without initiating formal consultation with the adherence specialist. Similarly, PCPs may have initiated the use of pill boxes and may have developed detailed written medication schedules without the involvement and knowledge of the adherence

specialist. If these interventions were provided by the PCP, they would not have been captured by the databases used in this study. Patients may also have received adherence education and counseling services from community case management organizations that receive Ryan White Grant funding specifically for these purposes. Similarly, these interventions could not have been measured and included in this study.

Based on the embedded procedural and administrative processes associated with the ADAP, it seemed likely that clients in this program would demonstrate greater utilization of adherence services and intervention then the usual care group. In this study, utilization of adherence services between the two groups was comparable. It is possible that PCPs and other staff were accustomed to providing adherence support to patients in the SAI group and consequently extended these interventions to all patients as a component of routine care. Healthcare providers may have had little knowledge of the patients' method of medication access and consequently delivered comparable services to all patients within the normal course of health care delivery.

Surprisingly, there were no significant differences in pharmacy refill adherence, self-reported adherence, and HIV RNA response related to ARV pill burden. While the literature supports improved adherence with lower pill burden, this study showed comparable adherence and treatment outcomes regardless of ARV pill burden. The largest percentage of subjects (48.1%) had a pill burden of 5-8 ARV pills per day while only 11.1% had daily pill burden of 9-15 and 43.2% received 2-4 per day. Although immunologic response based on pill burden was similar whether subjects received 2-4 or 5-8 pills per day, a higher percentage of subjects experienced CD4 decline when daily pill burden exceeded 8 pills (Chi-square 8.719, df 2, p=.013).

Pill burden for treatment of other health disorders such as diabetes, psychiatric conditions, cardiovascular and metabolic disorders was not assessed in this study. It is possible that HAART bill burden was minimal compared to pill burden associated with the treatment of other health conditions. Measurement of overall pill burden may better explain any potential differences in adherence and treatment outcomes.

Study Aim Two

The second study aim was to determine whether patients participating in the SAI program experienced improved response to treatment compared to patients receiving usual care, controlling for HIV disease-specific factors, ARV-specific factors, and socio-demographic factors.

To answer the first research question, "Is there a difference in CD4 lymphocyte response in subjects participating in the SAI program compared to those who receive usual care?" logistic regression was performed to test the null hypotheses that there were no differences between CD4 lymphocyte response in the usual care group of subjects and the subjects participating in the SAI. After controlling for covariates, there were no significant differences between the two groups and the null hypothesis was supported (OR 1.402; CI: 1.402,2.102; p = 0.102).

This unexpected finding may be explained by several factors. Most notably, expected CD4 lymphocyte response occurs more slowly compared to HIV RNA response which occurs more rapidly when initiating ARV therapy (Bartlett & Gallant, 2005; Nieuwkerk & Oort, 2005). It is likely that a six-month observation period may have been inadequate to fully appreciate the immunologic response to therapy. CD4 lymphocytes are also affected by diurnal and seasonal variations. Some clinicians prefer to monitor

the percentage of CD4 lymphocytes rather than the absolute number (Bartlett & Gallant, 2005), but not all laboratories provide this additional measurement. Unfortunately CD4 percentages were not available in this study. The subjects in this study also included a broad mix of clients at all ranges of HIV disease. Patients starting initial therapy would be expected to have a robust CD4 lymphocyte response while it would be unlikely for those chronically infected and on long-term therapy to experience a significant response. Lastly, the sample size was lower than expected and there may not have been enough power associated with this sample size to detect a small change in the CD4 lymphocyte response.

To answer the final research question, "Is there a difference in HIV RNA response in subjects participating in the SAI program compared to those who receive usual care?" logistic regression was performed to test the null hypotheses that there were no differences in the HIV RNA response between the two groups. After controlling for covariates, subjects who participated in the SAI program were over four and a half times more likely to achieve a favorable virologic response (OR 4.573; 95% CI 2.953, 7.080; $p<.0005$). There was a statistically significant difference between the two groups and the null hypothesis of no difference between the groups was rejected.

Limitations of the Study

There are several limitations to consider in this study. Each of these will be reviewed in the following section.

The sample was biased because all subjects were already enrolled in an AIDS drug assistance program and they all received care from one outpatient clinic. Additionally, all subjects received medication from one pharmacy. Clinical, pharmacy

and medication access programs were all at the same site. As a result, the findings may not be representative of the true population in the state-wide ADAP. The sample did represent racial and ethnic diversity consistent with HIV-infected patients within the local community.

Another source of bias is related to self-reported measurement of adherence. Although self-report is one of the most common methods of assessing medication adherence, inaccuracy may result due to imprecise or inconsistent questioning, patient forgetfulness and poor recall, or the patient's desire to provide socially desirable responses along with a desire to please the healthcare provider and prevent criticism. Consequently, when self-reporting methods are used to assess adherence, levels are frequently over-estimated.

The retrospective research design was purposely selected to minimize several possible confounders that existed in the years 2006 and 2007. Medicare D prescription drug plans were initiated in January 2006. Clients experienced unique barriers to medication access, unexpected loss of previous healthcare benefits and interruptions in their supply of medication. While most of the Medicare D complications resolved by 2007, eligibility requirements for Florida ADAP and other local funding plans occurred in 2007, once again disrupting the normal operations of ADAP.

A priori power estimates suggested a minimum sample size of 678 subjects were required for power of 0.80. A large number of potential subjects were unexpectedly excluded from analysis because they did not use the on-site pharmacy. Consequently, this study is inadequately powered to detect the effect size specified in the research design.

The findings of this research may not be generalizable to other populations. The sample of the participants may not reflect the overall population of those with HIV since the study site was a public clinic frequently used by those who are indigent or have public insurance such as Medicare or Medicaid. Patients with commercial insurance tend to seek private practices for their HIV care, so those employed in jobs that provide insurance were underrepresented in this sample, as well as those with high income. These findings cannot be applied to populations that were not represented in the subject groups. Further studies are recommended across various geographic areas, ethnic areas and other clinical settings.

Although this study examined a number of covariates, it is possible that there are unknown or additional variables that might impact adherence and treatment outcomes in this population. Examples might include level of education, social support, quality of life, number of previous antiretroviral regimens, presence of ARV resistance, and participation in a clinical drug study. Adherence education and counseling provided by case managers in the community may also have an effect on pharmacy refill adherence, self-reported adherence and treatment outcomes.

The short time of follow-up may have limited the ability to measure the long-range effect of the SAI. Although the relatively short follow-up time in this study may be inadequate to fully appreciate the virologic and immunologic response to therapy, extending the study period might result in additional confounders. For example, the population utilizing this public clinic is often transient, incarcerated and often lost to follow-up.

This study examined multiple variables that could impact both treatment response and adherence. It is difficult to attribute the true effect of each variable. Future study using path analysis might elucidate the true effect of each covariate.

Three types of antiretroviral therapy were considered in this study: (1) non-nucleoside reverse transcriptase based; (2) protease inhibitor based; and (3) triple nucleoside reverse transcriptase based. The protease inhibitor (PI) ritonavir is frequently administered in a low-dose along with a primary PI as a pharmacokinetic booster to the primary PI. Boosting a PI with ritonavir increases drug exposure and prolongs the plasma half-life of the primary protease inhibitor. This allows for reduced dosing frequency and pill burden and may improve overall adherence to the regimen (National Institutes of Health, 2006). Ritonavir-boosting was not assessed in this study and may be an important characteristic to assess in future studies since boosting can improve adherence through reduced pill burden and greater drug exposure could result in improved virologic and immunologic treatment response outcomes. Nelfinavir is the only protease inhibitor that cannot be effectively boosted by ritonavir (Bartlett & Gallant, 2005). Since a number of subjects received nelfinavir as a component of HAART, it may be helpful to study both boosted and unboosted PI-based regimens.

This study included patients who only used one consistent pharmacy to obtain their medication. A large number of patients (n=569) used alternative pharmacies throughout the community. Although the demographic characteristics of this population are similar to the sample of patients in the usual care group, the pharmacy refill adherence rates are not known. Future studies should consider investigating the pharmacy refill rates at community pharmacies to investigate whether there are any

unique features from the on-site pharmacy compared to community pharmacies. Since the dedicated on-site pharmacy is used to providing adherence messages within general conversation with patients, it is theoretically possible that even this communication may have an effect on patient adherence to medication therapy. It is not known what type of adherence messages or encouragement is provided by community pharmacies.

There was little effect on adherence related to active substance abuse and mental health disorders despite literature which supports a negative impact on adherence. The lack of effect in this study may be related to the coding of the substance abuse and mental health diagnoses or the small sample size. The covariates related to mental health and substance abuse were based on healthcare provider coding and documentation in the medical record. There were no clearly defined objective or operational definitions related to these diagnoses. It is possible that these diagnoses were under-diagnosed, over-diagnosed or misdiagnosed.

Significance

This study demonstrates a significant effect on self-reported adherence, pharmacy refill adherence, and HIV RNA response associated with participation in the AIDS drug assistance program. There are potential unknown covariates that may be involved with adherence and future qualitative inquiry may be helpful in identifying them and their potential effect on adherence. This will be discussed in another section.

Funding for AIDS Drug Assistance Programs is provided by the federal government and often supplemented with individual state funds. With limited national and state funding for these programs, it is imperative that funds be used as effectively as possible to serve the greatest number of clients possible and to produce the most optimal

clinical outcomes. This study demonstrates significant improvement in medication adherence as well as treatment outcomes associated with participation in one ADAP and can serve as a model to local, regional and national programs as a potential means to optimize medication adherence and treatment response with limited resources.

In the State of Florida, a centralized database contains administrative and clinical data related to each ADAP participant including CD4 lymphocyte counts, HIV RNA results, antiretroviral specific information and sociodemographic information. The findings from this study can serve as a starting point for program administrators to analyze statewide data to identify treatment response rates and program effectiveness. Additionally, administrators could utilize this database to identify problematic areas or areas that may need additional resources based on observation of clinical outcomes as measured by CD4 lymphocyte and HIV RNA response.

Ongoing discussion is occurring on a national level related to the collection and study of clinical outcome data from the various AIDS Drug Assistance Programs within the United States. This study demonstrates the potential benefit from examining these types of data and the potential benefits for program administrators, clinicians and patients.

Components of the structured adherence program may be appropriate for settings with limited technology or limited resources. Closely monitoring pharmacy refills and proactively implementing communication with patients before they run out of medication may be quite appropriate for rural or even sites in the developing world in an effort to improve adherence and treatment outcomes.

This study contributes to our knowledge of the difficulties in fully understanding the patient-level determinants of ARV medication adherence. There are numerous variables that affect adherence and ongoing research is indicated to continue to increase our understanding of this complex process. Results of this study provide a foundation for future research exploring issues of medication adherence, pharmacy refill adherence, and participation in structured medication access program.

It is important that the findings from this study are communicated to local staff involved in the study as well as the administrators at the regional, state and national level. The findings clearly support better adherence and clinical outcomes in the population participating in the medication access program. By disseminating this information to clinicians and administrators, others may be encouraged to implement similar procedures for monitoring pharmacy refills and initiating structured treatment intervention. With hundreds of medication access programs across the United States, it is important for clinicians and administrators to recognize the potential impact of their programs on adherence and treatment response.

Several immediate plans are in process to disseminate the findings of this study. Locally, the staff associated with the study site will be informed of the findings. On a community level, attendees at the local Association of Nurses in AIDS Care meeting will be provided with an overview of the study and its findings. At a regional level, the study results will be presented to a coalition of government representatives, corporations and community advocates representing fourteen southern states and their respective ADAPs. Lastly, the study will be submitted for publication in peer-reviewed journal.

Implications for Nursing Practice

The findings of this study support the ability of a structured adherence intervention within a medication access program to effectively influence clinical outcomes and adherence associated with the treatment of HIV-infected patients. Nurses and other healthcare providers play a key role in providing ongoing education related to ARV medication including proper administration, management of medication side effects, adherence to therapy, and adherence to clinical care. Nurses are in a key role to formally and informally assess adherence and to refer patients for specialized adherence education and counseling as needed. Nurses often have more contact with the patient than any other member of the health care team and are in a pivotal position to assess adherence and implement creative strategies to improve adherence and increase knowledge.

Nurses should have strong interviewing skills to be able to elicit information regarding adherence in a professional and nonjudgmental manner. Nurses are in a key role to recognize nonadherence and initiate appropriate adherence interventions as quickly and effectively as possible.

Nurse practitioners (NPs) continue to serve as primary care providers for many patients with HIV infection and are instrumental in initiating and managing antiretroviral therapy. By providing thorough patient education, selection of tolerable agents that the patient is able to adhere to, and prompt referral to adherence specialists, NPs can influence adherence in a positive and proactive manner. Nurse researchers are active in adherence research and continue to contribute to this growing body of knowledge.

There continues to be an ongoing need to develop effective adherence interventions and to increase awareness related to the importance of medication adherence among patients living with HIV disease. It is important to find adherence interventions that are cost-effective and replicable outside of a research setting.

It is equally important to encourage ongoing educational activities for patients, nurses, and other health care providers to increase their knowledge and awareness related to medication adherence and pharmacy refill adherence as a means to improve immunologic and virologic success with HAART.

There is a growing need for effective patient education regarding readiness for treatment, HIV illness management, drug-drug interactions, potential drug side effects and side effect management. The complexity of treatment and the side effects of treatment make this an important area for nursing practice. Similarly, there is a need for further development of a standardized definition of adherence and valid objective measures of adherence that are appropriate for both clinical research and clinical care settings. Future research needs to address the best method to assess adherence to ensure reliability and validity, since this is the crucial outcome measure in all adherence research and because adherence has a direct impact on patient morbidity and mortality. The self-report method of measuring adherence may not be the most useful predictor of adherence.

Recommendations for Future Study

Based upon the review of related studies and the findings from this study, a number of recommendations are made for future research in this area. This study could be replicated using a prospective design with a larger sample size that encompasses different geographic areas and which follows subjects for a longer time period. This

would generate findings that would be more representative of the population with HIV and AIDS and would have the power to more accurately measure the effects of covariates associated with adherence and treatment response. It would be helpful to measure HIV RNA response and CD4 count response as a continuous variable over many months to many years. Inclusion of CD4 lymphocyte percentage may be an additional variable to consider in the study. A longitudinal study design might permit longer follow-up to determine if adherence and treatment outcome responses are retained for long periods of time.

Future studies should consider distinguishing between ritonavir boosted protease inhibitor based regimens and non-ritonavir boosted PI regimens. Although non-boosted PI regimens are becoming less common, there were a significant amount of nelfinavir based regimens in the study (non-boosted). Non-boosted PI regimens are traditionally less potent and durable that boosted-PIs and may have less favorable treatment outcomes. While this study defined three types of antiretroviral therapy regimens (non-nucleoside reverse transcriptase based, protease inhibitor based, and triple nucleoside reverse transcriptase based), future studies should consider incorporating newer regimens that emerged in 2007 and 2008 including entry inhibitor based, integrase inhibitor based, and second generation NNRTI-based.

A qualitative research component would be very useful in future research. Qualitative inquiry may help to identify perceptions and behaviors associated with the SAI, other adherence strategies used by patients (such as cellular phone alarms, internet based systems, and other personal strategies), factors identified by the clinical population to be important in their adherence to medications, and the burden of chronic disease.

Qualitative inquiry involving staff of both the medication access program and pharmacy may also generate findings that influence adherence such as adherence messages delivered within the normal course of business communication, informal teaching messages, and other verbal and nonverbal messages.

Ongoing research in this field should include the study of clients that use community pharmacies as well as those that use pharmacies that deliver monthly medications directly to patients' homes. General community pharmacies (as opposed to community HIV-specialty pharmacies) may not be as knowledgeable about HIV treatment agents and may not understand the importance of high levels of adherence to medication refills. More pharmacies are offering free home delivery of HIV medications as a means to increase their business while providing a valuable service and convenience to patients. The adherence implications of these services have not been formally studied and published.

It is also important to consider the effect of community-based adherence educators on patient adherence and treatment outcomes. Although these programs are often funded by Ryan White Grant funding, they frequently operate with case management and social work agencies with little or no contact with medical care providers, AIDS drug assistance programs, and client pharmacies. Qualitative studies of these programs may provide important information that impact clinical care and pharmacy refill behaviors. As the population affected by HIV continues to impact more people of color and more minorities, it is important to consider the potential impact of cultural barriers and language barriers of subjects whose primary language is non-English.

While the findings of this study demonstrate improved adherence and treatment response associate with the ADAP, it would be beneficial to investigate the costs associated with the program and determine if the program is indeed cost-effective for the adherence and outcome benefits associated with the program. With dwindling federal and state funding of these programs, this information is critical in ensuring ongoing funding of these valuable programs.

Summary

The purpose of this retrospective comparative study was to better understand the effects of an existing antiretroviral access program on adherence to HAART and response to treatment compared to usual care. In the structured adherence intervention (SAI) providers closely monitored monthly HIV medication refills and provided structured adherence intervention when indicated. Patients receiving usual care were enrolled in a Medicaid-funded medication access program and did not receive ongoing medication refill monitoring and structured adherence intervention. Both patient groups received their ARV medications and outpatient HIV medical care from a single treatment center and pharmacy

Three of the four hypotheses were confirmed in this study. Patients participating in the SAI demonstrated higher levels of both self-reported and pharmacy refill adherence compared to patients receiving usual care. Patients in the SAI were almost four times more likely to self-report $\geq$ 90% adherence (OR 3.94, $p<.0005$) compared to the usual care group and almost twice as likely to achieve favorable pharmacy refill adherence (OR 1.83, $p=.005$). Although patients participating in the SAI program demonstrated better virologic (HIV RNA) responses to HAART compared to patients receiving usual care,

immunologic (CD4 lymphocyte) responses to HAART were not significantly different compared to subjects in the usual care program. Patients in the SAI were more than four times as likely to achieve a favorable HIV RNA response compared to those in the SAI (OR=4.57, $p<.0005$).

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Appendicies

Appendix A

USF
UNIVERSITY OF
SOUTH FLORIDA

September 19, 2007

Donald E. Kurtyka
15610 Indian Queen Drive
Odessa, FL 33556

RE: **Exempt Certification** for IRB#: 106158
Title: *The Effects of a Structured Adherence Intervention to HAART on Adherence and Treatment Response Outcomes*

Dear Mr. Kurtyka:

On September 19, 2007, the Institutional Review Board (IRB) determined that your research **meets USF requirements and Federal Exemption criteria 4, existing data, documents, records, pathological specimens, or diagnostic specimens publicly available or recorded without identifiers.** It is your responsibility to ensure that this research is conducted in a manner reported in your application and consistent with the ethical principles outlined in the Belmont Report and with USF IRB policies and procedures.

Please note that changes to this protocol may disqualify it from exempt status. It is your responsibility to notify the IRB prior to implementing any changes.

The Division of Research Integrity and Compliance will hold your exemption application for a period of five years from the date of this letter or for three years after a Final Progress Report is received. If you wish to continue this protocol beyond those periods, you will need to submit an Exemption Certification Request form at least 30 days before this exempt certification ends. If a Final Progress Report has not been received, the IRB will send you a reminder notice prior to end of the five year period; therefore, it is important that you keep your contact information current with the IRB Office. Should you complete this study prior to the end of the five-year period, you must submit a Final IRB Progress Report for review.

Please reference the above IRB protocol number in all correspondence to the IRB c/o the Division of Research Integrity and Compliance. In addition, we have enclosed an Institutional Review Board (IRB) Quick Reference Guide providing guidelines and resources to assist you in meeting your responsibilities when conducting human subjects research. **Please read this guide carefully.**

DIVISION OF RESEARCH INTEGRITY & COMPLIANCE
University of South Florida • 3702 Spectrum Blvd., Suite 155 • Tampa, FL 33612-9445
(813) 974-5638 • Fax (813) 974-7091

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-9343.

Sincerely,

Paul G. Stiles, J.D., Ph.D., Chairperson
USF Institutional Review Board

Enclosures: IRB Quick Reference Guide

Cc: Various B. Menzel, USF IRB Professional Staff
Gail Powell-Cope, PhD

SB-EXEMPT-0602

Appendix B

FLORIDA DEPARTMENT OF HEALTH

Charlie Crist
Governor

Ana M. Viamonte Ros, M.D., M.P.H.
State Surgeon General

INSTITUTIONAL REVIEW BOARD NON-RESEARCH DETERMINATION

September 10, 2007

Donald E. Kurtyka, ARNP-BC, MS, MBA
Hillsborough County Health Department
1105 East Kennedy Boulevard
Tampa, FL 33602

Protocol Title: The Effects of a Structured Adherence Intervention to HAART on Adherence and Treatment Response Outcomes

IRB Determination: Activity does NOT involve human subject's research

The Department of Health Institutional Review Board, or representative, determined, based on the information provided, your activity does not involve human subjects, as defined in DOH policy and federal regulation as, "a living individual about whom an investigator conducting research obtains data through intervention or interaction with an individual or the individual's identifiable private information" (§ 45 CFR 46.102(d)).

As a reminder, if there is a change in the activity, IRB review may become necessary. If you have questions about whether your activity may require IRB approval, please contact the IRB administrative office so we may determine whether the additional activities come under the category of research.

If you have any questions, or if we can be of any assistance, please contact the Department of Health IRB at (850) 245-4585 or toll-free in Florida (866)-433-2775. You may also visit our website at: http://www.doh.state.fl.us/execstaff/irb/

Thank you for your cooperation with the IRB.

Sincerely,

Robert Hood, Ph.D.
Assistant Director
Office of Public Health Research

Federal Wide Assurance#: 00004682

Office of the State Surgeon General
4052 Bald Cypress Way. Bin A00 • Tallahassee. FL 32399-1701

About the Author

Donald E. Kurtyka received a Bachelor of Science degree in Nursing from Fitchburg State College in 1980, a Master of Business Administration degree in health care management from Western New England College in 1983, and a Master of Science degree in Family Health Nursing from the University of South Florida in 1992.

As a board certified Family Nurse Practitioner he maintains a clinical practice in the specialty of HIV/AIDS care. He is an instructor in the University of South Florida's College of Medicine, Division on Infectious Diseases and International Medicine and Director of HIV Services for Tampa General Hospital. Dr. Kurtyka is certified as an HIV Specialist by the American Academy of HIV Medicine.