HIV Medication Adherence: Reasons for Missed Medication and Rethinking the Trajectory

by

Jennifer Geralyn Okonsky

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

DEDICATION

This dissertation is dedicated to my Mother, my sister Denise, my niece Hannah, my daughter Ella, and my husband Jesse. Their unconditional love, support and patience provided the pillars for this accomplishment.

ACKNOWLEDGEMENTS

I would like to extend my deepest appreciation to Dr. Carmen Portillo, my doctoral advisor. Her continued support, patience and confidence enabled me to stay motivated and enthusiastic about my work.

I extend my gratitude to the members of my dissertation committee Dr. Carol Dawson-Rose and Dr. Mallory Johnson. Their guidance and mentorship has contributed to my academic growth.

I also want to acknowledge Dr. William Holzemer, my qualifying exam chair for his expertise and keen scholarship.

I wish to acknowledge Dr. Eric Vittinghoff and Dr. Bruce Cooper for their assistance with data analysis.

Thank you to all of the study participants, clinics and organizations that were instrumental in completing this work.

Lastly, I am most grateful for the unending support, wisdom and encouragement offered by Dr. Allison Webel.

This dissertation was supported by: National Institutes of Health Training Grants: T32NR007081 and T32RR023259.

Chapter 2 of this dissertation is a reprint of the material that appears in: Okonsky, J. G. (2011). Problems taking pills: understanding medication adherence from a new perspective. *AIDS Care, 23*, 1652-1659.

ABSTRACT

HIV MEDICATION ADHERENCE: REASONS FOR MISSED MEDICATION AND RETHINKING THE TRAJECTORY

Jennifer G. Okonsky, RN, MA, PhD

University of California, San Francisco, 2011

HIV medication adherence is critical for HIV viral suppression and reducing morbidity and mortality. Adherence rates are below optimal levels and women have poorer adherence compared to men. Fifty percent of people treated with antiretroviral therapy (ART) are resistant to at least one medication. Current interventions are costly and magnitude of improvement is often small. Three studies were conducted to examine the reasons why people are missing their medications and the relationship with documented factors. The first study examined key correlates and reasons for missed medication in people from nine cities in the US using an ordinal regression model. Problems taking pills (PTP), (a factor of five reasons) was significantly associated (p=.003) with use of a protease inhibitor (PI) regimen. A person taking a PI regimen is 1.7 odds of having more PTP versus a non-PI based regimen. Symptom experience (OR: 3.8; 95% CI: 2.7, 5.2) and other health conditions (OR: 0.7; 95% CI: .45, .98) were found to be independently associated with PTP. The second study's purpose was to examine and gain an appreciation of the reasons why HIV infected women taking ART in the US are missing their HIV medications, and how the results can influence a

new trajectory of adherence research. Women were 2.2 times more likely to document reasons pertaining to forgetfulness than PTP, (OR= 2.2, 95% CI: 1.63, 2.94, $p<0.001$). There was a difference between the adherent and non-adherent groups in reasons for missed medications given overall, but no difference between those on a PI-based versus a non-PI-based regimen. The final study examined women using a self-management framework and analyzed reasons for non-adherence according to contextual, process and outcome factors. The reasons, 'wanting to avoid side effects' and 'being away from home' were found to have a significant difference when associated with race and employment. The three studies suggest translating the evidence of a common profile of non-adherence into a proactive individual discussion, engaging the patient-provider relationship to appreciate the reasons for intentional or unintentional non-adherence and offers a self-management framework to organize adherence discussions and intervention development.

TABLE OF CONTENTS

CHAPTER FOUR: UNDERSTANDING NON-ADHERENCE IN WOMEN

CHAPTER FIVE: DISCUSSION

LIST OF TABLES

LIST OF FIGURES

Introduction

The year 1981 marked the official beginning of the HIV and AIDS epidemic (US Department of Health and Human Services, 2011a). In the United States (US), 1.2 million people are living with HIV and women represent 25% of the newly diagnosed cases of HIV (Centers for Disease Control and Prevention, 2011). In March of 1987, the US Federal Drug Administration (FDA) approved the first antiretroviral drug, and in August of 2011 we have thirty-five antiretrovirals approved by the US FDA (US Department of Health and Human Services, 2011b). Clinical trials have been conducted and continue to validate the use of antiretrovirals in the treatment of HIV/AIDS. The treatment goals of HIV/AIDS integrate biological and clinical indicators; HIV-1 RNA viral load suppression, restoration of the immune response (CD4 cells), slowing the progression of the disease, increased survival rates, reduced morbidity and a better quality of life. Antiretroviral therapy (ART) provides a regimen that inhibits areas of the HIV life cycle replication, provides for HIV viral suppression and an increase in immunological function. Adherence is critical for HIV viral suppression and delaying progression of AIDS (Crane et al., 2006; Oyugi et al., 2004; Stevens, Kaye, & Corrah, 2004). It has been accepted that HIV and ART are exceptional in that adherence rates of $\geq$ 95% are required to prevent drug resistance, treatment failure and sustain viral suppression (Gill, Hamer, Simon, Thea, & Sabin, 2005; Low-Beer, Yip, O'Shaughnessy, Hogg, & Montaner, 2000; Paterson et al., 2000). However, later studies reported that lower levels of adherence could provide viral suppression with more potent drug regimens (Bangsberg, 2006; Maggiolo et al., 2005). In spite of these later findings, it is

critical for persons to achieve the highest possible level of adherence to optimize HIV treatment goals. Although ART has changed HIV from a fatal to a chronic disease, non-adherence is a major barrier. HIV/AIDS and adherence to ART is a multifaceted problem that needs a multi-layered approach. Gaining an understanding why people adhere and do not adhere to their medications, improving upon strategies and developing interventions that will increase or maintain adherence remains a challenge and an essential research focus.

Statement of the problem

Adherence is dynamic and the behavior is complex. HIV medication adherence rates are below optimal levels and worse for women compared to men. Adherence research is vital to the health of people living with HIV and AIDS. Non-adherence to ART can result in lives lost and a drug resistant epidemic. Up to 50% of people treated with ART now have strains of HIV that are resistant to at least one of the available antiretroviral drugs. As researchers, we need to gain a better understanding of the dynamics of adherence behavior and develop interventions that are accessible, appropriate and feasible to support persons taking ART.

Purpose

Researchers, clinicians and persons living with HIV and AIDS need to better understand reasons for non-adherence and their association with documented factors within the published adherence literature. The purpose of this dissertation is to examine the reasons why people who are taking antiretroviral therapy are missing their

medications and the relationship with documented factors. The goal of this dissertation is to contribute to the scientific literature and provide evidence that can influence a new HIV trajectory of adherence research and intervention development.

This dissertation analyzes reasons for non-adherence using an evolutionary approach in order to reach an increased understanding of adherence behavior and introduce a framework that can support translational research. It will elucidate adherence behavior from a secondary analysis with men and women from nine cities in the US as well as two additional analyses focused on women living in two cities in the US.

Background

Medication adherence has been an area of concern for many decades with patients, health care providers and researchers primarily in the health care areas of hypertension, diabetes, antibiotic treatments and many psychiatric conditions. In fact, Hardy (1948) published the first adherence study 63 years ago in the Journal of the American Medical Association. Although there has been over 60 years of adherence research in various fields, it remains a complex issue. A Cochrane review published in 2008 reported less than half of doses are taken by people who are prescribed self-administered medications (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008). It is documented in the United States and in Europe that estimates of the prescribed HIV medication doses taken range from 60-70% (Simoni et al. 2006). Mills et al. (2006) conducted the first systematic meta-analysis of adherence levels in Sub-Saharan Africa (SSA) with adherence levels in North America (NA) in order to relate the findings found in SSA programs to more established programs. Both reported similar thresholds of

adherence (80-100%) and a pooled analysis of 55% in NA achieved adequate levels of adherence and 77% estimate in SSA. Of these studies in NA 71% used self-reported measures to assess adherence and 66% of the African assessments used self-report.

HIV medication adherence is unique in a variety of ways. One is the overall difficulty with adherence to HIV medications and another is the consequence of not adhering. Adherence is a complex behavior that is subjected to characteristics of the HIV virus, patient, environment, social context, clinical setting, treatment regimen, patient – provider relationship and the overall dynamic nature of change. Holtgrave & Pinkerton (1997) estimated the lifetime costs associated with an HIV infection are as high as US $195,000 and that was more than 10 years ago. As cited in Simoni, Frick, Pantalone, & Turner (2003) adherence is defined as: "The ability of the person living with HIV/AIDS to be involved in choosing, starting, managing, and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function" (p.185). Although there is no universally accepted definition of adherence, this definition provides the main elements. However, the weakness of the definition is that it does not consider structural barriers (i.e. access) that may decrease adherence due to obstacles that are beyond the control of the patient. Access, in this context can refer to accessible transport (inclusive of money to access transport), availability of medicines (stock of medicines) and access to affordable medicines as well as access/right to be relieved from work.

Non-adherence to HIV medication can result not only in poor clinical outcomes but is also a concern in the public health arena. There is the general threat of HIV-infected persons transmitting the virus to another, but yet another great threat of

nonadherent infected persons transmitting a resistant strain of the virus. The treatment for HIV was initiated using monotherapy (one drug), but with the on going clinical trials and bench science monotherapy has become an outdated treatment and combination therapy is now the norm. The last 10 years of research has also provided combination pills with once a day dosing supporting less pill burden and less doses per day. The focus of targeting the virus at different phases during the life cycle brought with it increased viral suppression, but also pill burden, dietary restrictions, and side effects which brought the potential for decreased adherence that in turn led to drug resistance. Little et al (2002) reported that in 1995 through 1998, 3.4% of treatment-naïve patients that had a > 20 fold reduction in susceptibility to all classes of HIV medications. During 1999 to 2000, 12.4 % of treatment-naïve patients had a >20 fold reduction in susceptibility to all classes of HIV medications, so within 5 years there was a 9% increase of patients who were already limited in their drug regimen selection, and this is likely due to non-adherence.

Overall, decades of research has shown that adherence to antiretroviral therapy (ART) is the key to HIV treatment success (Paterson et al., 2000; Wood et al., 2004). Optimizing adherence increases the time of effectiveness of the drug, is cost effective and improves quality of life. The consequences of non-adherence to ART leads to drug resistance and eventually treatment failure and potentially results in an epidemic of drug resistant HIV (Clavel & Hance, 2004). Drug resistance is challenging to treat and more costly. Non-adherence can lead to more hospitalizations, poor health outcomes and low quality of life (Bangsberg et al., 2001; Sax, Meyers, Mugaver, & Davis, 2010). Continued research in the field of medication adherence remains a vital research focus.

HIV Adherence Literature Review

A plethora of HIV adherence research using quantitative methods has been published examining the many factors associated with taking antiretroviral therapy. Determinants of non-adherence, facilitators and barriers to adherence, the experience of taking HIV medication, patterns, correlates and predictors of adherence, patient and regimen characteristics have all been described in the literature and have provided a strong body of evidence to assist researchers, health care providers and people living with HIV and AIDS in gaining an understanding into HIV medication adherence behavior (Ammassari et al., 2002; Atkinson & Petrozzino, 2009; Barfod, Sorensen, Nielsen, Rodkjaer & Obel, 2006; Catz, Kelly, Bogart, Benotsch & McAuliffe, 2000; Chesney et al., 2000; Deloria-Knoll et al.,, 2004; Heckman, Catz, Heckman, Miller & Kalichman, 2004; Kyser et al., 2011; Protopopescu et al., 2009; Sullivan et al., 2007).

Table 1: Factors associated with adherence

Barriers	Facilitators
• Substance abuse • Anxiety • Depression • Complexity of regimen • Mistrust in HIV medicines • Perceived side effects • High Pill burden • Greater number of doses per day • Work and family responsibilities • Limited access to ART • Stressful life events • Speaking a different language then health care provider • Mistrust of providers • Lack of social/family support • Fear of disclosure • Denial of HIV • AIDS diagnosis	• Self-efficacy • Social support • Acceptance of HIV diagnosis • Understanding the need for adherence • Knowledge of treatment benefits • Positive effects of ART • Perceived effectiveness of ART • Sharing treatment decision making • Strong intention to adhere • Reminder tools • Regimen that fits into daily routine • Once daily dosing • Motivational readiness • Patient-provider relationship • Strong will to live • Fewer years of HIV • Fewer year on ART

Although the majority of the findings have been documented through quantitative approaches, qualitative methods have also contributed to the adherence literature (Barfod, Hecht, Rubow, Gerstoft, 2006; Beusterien, Davis, Flood, Howard, & Jordan, 2008; Konkle-Parker, Erlen, & Dubbert, 2008; Kremer, Irnoson, & Porr, 2009, Mohammadpour, Yekta, Nikbakht Nasrabadi, 2010; Sankar, Golin, Simoni, Luborsky, Pearson, 2006; Steverns, Hildebrandt, 2009; Wayson Locher, Pargament & Duggan; 2008).

The majority of qualitative studies document their findings in terms of the themes that were described. A 2003 qualitative study conducted by Remien et al. with 110 men and women from four US cities not only presented themes that were revealed through the interviews but also an overall impression. They found that most of the participants were describing adherence as a "dynamic phenomenon that changes over time with their changing beliefs, attitudes, emotions, and daily and larger life events" (p.64). While the dynamic nature of adherence is well accepted by researchers and providers, it is substantial that the participants of the study articulated this particular characteristic as well. Themes from this study included: belief and trust in ART and health care providers, intentional non-adherence (experience of side effects and concerns about toxicity), self-monitoring, role of substance abuse, regimen demands, priorities, competing concerns, social supports, and ambivalence toward medication. Sankar, Golin, Simoni, Luborsky & Pearson (2006) conducted a review of all qualitative studies published between 1995 and January 2006. Although the focus areas varied considerably they grouped the 66 studies into four topic areas: challenges, barriers and facilitators, adherence practice, values and beliefs, and the lived experience. Research conducted from January 2006 until now seem

to follow the same topic areas. Lewis, Colbert, Erlen & Meyers (2006) conducted a qualitative study with men and women from Pennsylvania who were 100% adherent and overall found that managing certain areas of adherence (regimen, self and environment), adopting realistic expectations and pragmatic attitudes, making medication a priority, believing in the efficacy of medications and a strong patient/provider relationship were the themes that allowed for successful medication management. Themes from a 2008 study (Konkle-Parker, Erlen & Dubbert) conducted in the Deep South revealed acceptance of diagnosis, consequences of non-adherence, prayer and spirituality, and social support to be facilitators. The barriers included denial, life stress, social stigma, side effects of medicine and shame. Stevens & Hilderbrandt (2009) conducted a qualitative study with women living with HIV who 'had persistent difficulties adhering' to ART. The findings suggested that there intentional non-adherence was personally meaningful, for a good purpose and 'guided by the rationales and principles women lived their lives by'.

Bridging quantitative and qualitative adherence research offers a holistic view of the vast body of literature. This holistic view plays a pivotal role for increasing the understanding of barriers, facilitators, values, beliefs and lived experiences for people living with HIV and AIDS taking ART. This view is instrumental when developing feasible and appropriate adherence strategies and interventions to sustain and improve HIV medication adherence.

Women and HIV Adherence

Twenty-five percent of the newly diagnosed cases of HIV in the US are women (Centers for Disease Control and Prevention, 2011a). Studies on women living with HIV have reported poorer medication adherence compared to men (Arnsten, et al., 2002; Lopez, Jones, Villar-Loubet, Arheart & Weiss, 2010; Puskas et al., 2011; Ubbiali et al., 2008). HIV adherence literature on women has steadily grown in the last decade (Holstad, Dilorio & McCarty, 2011; Howard et al., 2002; Jones et al., 2003; Knowlton et al., 2011; Murphy, Greenwell & Hoffman, 2002; Meyer, Springer & Altice, 2011; Roberts & Mann, 2003;Vyavaharkar et al., 2007; Wayson Locher, Pargament, & Duggan, 2007; Webel, 2010; Webel & Higgins, 2011). In 2002, Murphy, Greenwell & Hoffman published a study focused on factors associated with adherence among HIV-infected women with children. Rates of adherence in this sample of 46 women with children ranged from 43% to 56%. Alcohol use, perceived stress, having a partner, age of youngest child, poor self-efficacy to stay with treatment, and poor outcome expectancies regarding the benefits of following treatment regimen were factors associated with non-adherence. Howard et al., (2002) conducted a large prospective study of adherence in a multi-center cohort of HIV-infected women. Factors they found that were predictive of lower adherence included: active drug use, alcohol use, frequent medication dosing, shorter duration on HIV medications, younger age and lower initial CD4 lymphocyte count. Howard et al., (2002) also found that adherence varied significantly over time, a mean of 64% at month one to 45% in month six. Jones et al., (2003) in a sample of 174 women from three US cities found that greater participant knowledge regarding HIV, HIV medications, and the immune system was related to higher HIV medication

adherence. Coping by denial, substance use, and behavioral disengagement were associated with lower HIV medication adherence.

Roberts and Mann (2003) studied 20 women between the ages of 25 and 54 living with HIV in the US, and collected women's own perceptions in diary format to better understand why these women intentionally fail to adhere to their ART. Intentional non-adherence refers to the deliberate aim not to take medications, and it occurs when patients who are knowledgeable about the medications choose not to adhere. Roberts and Mann (2003) suggest that intentional non-adherence is very emotional and adherence decisions are continually renegotiated. They underscore the need for routine provider-patient adherence communication. Researchers and clinicians are highlighting the need for enhanced communication strategies and patient-centered approaches to improve ART adherence management (Rochon et al., 2011; Saha, Beach, & Cooper, 2008; Wilson, 2010). Wayson Locher, Pargament & Duggan, (2007) interviewed seven women of color and three themes emerged: trust/mistrust (partners, providers and health system, medication), approach/avoidance motivation (to take medication) and constantly tethered (to the disease, medications).

Despite the increased focus on women, adherence and HIV, and some consistency in the findings, there still remains a gap in understanding how best to address adherence in women. As women continue to struggle with managing not only HIV/AIDS but other chronic diseases (Phillips, Neaton , & Lundgren 2008), it is critical to continue gathering evidence, quantitatively and qualitatively, in order to support women in managing their disease(s). Exploring the role of intentional non-adherence and provider-patient

communication are key areas to address in order to offer a holistic view of adherence and women.

Reasons for Non-Adherence

HIV medication adherence literature often reports the reasons why people miss their medications (Chesney, 2003; Gay et al, 2011; Heckman, Catz, Heckman, Miller & Kalichman, 2004; Kyser et al., 2011; Sullivan, Campsmith, Nakamura, Begley, Schulden & Nakashima, 2007), with forgetting and side effects among the most common. However, only selected researchers have examined the association of reasons for missed medications with HIV medication adherence (Amico et al., 2007; Barfod et al., 2006; Ferguson et al., 2002; Kalichman, Catz & Ramachandran, 1999; Okonsky, 2011; Vyavaharkar et al., 2007; Walsh, Horne, Dalton, Burgess & Gazzard, 2001). Examining the relationship between reasons for non-adherence and reported factors affecting adherence will expand the profile of adherence literature. Kalichman et al. (1999) linked low education literacy in African American adults with decreased adherence in relation to confusion about medications, sleeping through a dose, and feeling depressed or overwhelmed. Exploring the difference in reasons between adherent and nonadherent persons was studied by Catz et al. (2000) & Barfod et al. (2006). Ferguson et al. (2002) analyzed reasons and the association with gender and race. Walsh et al. (2001) examined protease inhibitor regimen and frequency of reasons. Amico et al. (2007) investigated how gender, employment, depression and education impacted reasons for adherence. Vyavaharkar et al. (2007) focused on HIV infected women with depression. The study

examined the relationships among sociodemographic factors, social support, coping, and adherence (reasons for missed medication and self-reported adherence).

The importance of appreciating the reasons for non-adherence can assist in overcoming barriers to ART non-adherence. While the research on reasons for non-adherence is growing, a gap still exists in bridging the reasons for non-adherence and a translatable framework to support optimal adherence within the dynamic phenomenon of adherence.

HIV Adherence Interventions

Research informs us that two hundred potentially relevant variables have been explored in-depth in regard to factors that influence HIV adherence behavior (Ramirez Garcia & Cote, 2003). The appreciation of promoting health behavior and health education interventions for individuals on ART are widely accepted and research specific to HIV adherence interventions have dramatically increased since 2002. Several reviews on adherence interventions have been published (Amico, Harman, & Johnson 2006; Cote & Godin, 2005; Fogarty et al., 2002; Ickovics & Meade, 2002; Simoni, Frick, Pantalone & Turner, 2003;Simoni, Pearson, Pantalone, Marks & Crepaz, 2006; Rueda et al., 2006; Sandelowski, Voils, Chang, & Lee, 2009). Amico, Harman, & Johnson (2006) published a research synthesis of trials on adherence interventions from 1996 to December 2004 and included effect size calculations. The review provided evidence that ART adherence interventions "seem to be moderately successful, but interventions that offer a compendium of resources and strategies for patients with diverse and changing ART adherence needs are likely hold the most promise" (p. 296). Rueda et al. (2006) published

a systematic review of the research literature on the effectiveness of adherence. Studies that used individual versus group, had periods of time > 12 weeks, and those interventions that targeted medication management skills (75% success rate) versus cognitive behavioral or motivational skills were more often associated with success. Simoni, Pearson, Pantalone, Marks, & Crepaz (2006) conducted a meta-analytic review of randomized controlled trials to assess the efficacy of interventions improving ART adherence and HIV-1 RNA viral load from 1996 through September 2005. The review sought to examine the effectiveness of behavioral interventions to increase patients attaining 95% adherence or an undetectable HIV-1 RNA viral load. Simoni et al. (2006) found that the "magnitude of the aggregated odds ratio (OR) indicated that participants who received an intervention were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load (VL) as participants in the control arm" (p. S30).

The overall consensus is that only a small proportion of the intervention studies meet acceptable levels of scientific rigor and most have small effects on adherence. Sandelowski, Voils, Chang & Lee (2009) completed a systematic review comparing descriptive and intervention studies to examine the extent to which the studies targeted the facilitators and barriers known to affect adherence. They did find congruence with substance abuse, family and provider support as factors identified in intervention studies. The review raised concerns regarding the tailoring, targeting and fidelity in adherence interventions and how best to capture the variations in people living with HIV, the social environment, type of medication regimen, and the understanding that adherence research is on going. Yard, Huh, King and Simoni (2011) discuss the "…efforts to improve

current ART adherence interventions should focus on creating flexibility that allows for adaptation to specific patients and their unique combination of adherence barriers, rather than attempting to adapt current interventions to specific patient subgroups".

A critical review of adherence interventions has provided the research community with a challenge. As the state of adherence is dynamic and the lives of people who are taking ART are also dynamic, an alternate path for adherence intervention and organization of the literature needs to be considered.

Self-management

Approximately half of all Americans are managing a serious chronic health condition at home (Centers for Disease Control and Prevention, 2011b). Research on self-management programs have been studied and proved effective in the areas of asthma, diabetes and arthritis, and very few with HIV, (Barlow, Wright, Sheasby, Turner & Hainsworth, 2002; Webel, 2010). One of the many ways self-management has been defined is, "the tasks an individual must undertake to live with one or more chronic condition. These tasks include having the confidence to deal with the medical management, role management and emotional management of this condition." (Barlow, Wright, Sheasby, Turner & Hainsworth, 2002, p.220). Self-management behaviors improve health outcomes, but not all researchers, academics, and providers agree on the components and how best to incorporate them in order to improve health. Ryan & Sawin (2009) present a descriptive mid-range theory to organize the similar and divergent ideas. They propose that self-management is a complex dynamic phenomenon consisting of three dimensions; context, process, and outcomes. The context dimension consists of

condition-specific factors, physical and social environments, and individual and family characteristics. The concepts of the process dimension are based in health behavior theories, research and practice. The concepts include: knowledge and beliefs, self-regulation, skills and abilities, and social facilitation. The outcomes dimension is inclusive of proximal and distal outcomes. The proximal outcomes are self-management behaviors and cost of health care services, while distal are health status, quality of life and cost of health. Incorporating the many factors affecting adherence into a self-management framework can provide a lens to view the dynamic nature of adherence. A self-management framework can provide the flexibility that will allow for the adaptation to individuals with common and unique barriers to adherence.

To this end, this dissertation will provide a new perspective when analyzing reasons for non-adherence, gain an appreciation for the reasons for non-adherence in women and integrate a self-management framework to organize how adherence can be viewed while rethinking the trajectory of adherence research.

Methods

This dissertation presents three papers that address HIV medication adherence, specifically, reasons for missed medication in people taking antiretroviral therapy. Each paper examines reasons for non-adherence from a different perspective. Each perspective provides another layer of information that in turn builds upon a program of research in HIV medication adherence. My program of research focuses on synthesizing the existing literature, gaining an understanding of the strengths, weaknesses, identifying the gaps and finally building on the existing literature in order to suggest recommendations for

improving how researchers can translate their findings and develop feasible and adaptable interventions. Each paper is presented in the format required by the journal to which it was submitted.

The first paper in this dissertation is, *Problems taking pills: understanding HIV medication adherence from a new perspective.* This paper examined several key potential correlates of reasons for missed medication in men and women living with HIV/AIDS from nine cities in the US. This paper used an ordinal regression model to examine reasons in relationship with regimen type, symptom experience, AIDS diagnosis, other health conditions and social support. This study revealed that problems taking pills (a factor that includes five reasons) versus forgetfulness (a factor of four reasons) was significantly associated with the use of a protease inhibitor (PI) regimen. A person, in this sample, taking a PI based regimen has a 70% increase of having more problems taking pills versus someone on a non-PI regimen. The study results offer a foundation that can add to the profile of reasons and non-adherence.

The second paper in this dissertation, *Not Just Simply Forgetting: Appreciating Reasons for Missed Medication in Women by Adherence Level and Regimen,* describes the importance of appreciating the reasons for non-adherence in women by adherence level and type of regimen. The purpose of this study was to examine and gain an appreciation of the reasons why women living with HIV taking ART are missing their medications, and how the results can influence a new trajectory of HIV ART non-adherence research.

The sample included 206 women from two cities in the US taking ART. In this sample, women were 2.2 times more likely to document reasons pertaining to

forgetfulness than problems taking pills. A significant difference was found between the adherent and nonadherent groups in reasons for missed medication overall, but no difference between those on a PI based regimen vs. non-PI based regimen. Results from this study suggest that a patient-centered approach that reviews type of reasons, frequency of reasons and type of non-adherence (intentional vs. unintentional) can support development of novel adherence interventions.

The third and final paper in this dissertation, *Understanding Reasons for Non-adherence in Women living with HIV and AIDS Using a Self-Management Framework,* describes reasons for non-adherence in women using a framework from Ryan and Sawin's Individual and Family Self-Management Theory. Examining the reasons using a self-management framework is applicable to women living with HIV who are often managing several conditions and balancing multiple social and family roles. The purpose of this study was to explore the reasons of non-adherence and the influence of selected contextual, process and outcome factors. Demographic and clinical characteristics (race, education, employment, regimen, AIDS diagnosis) along with access to care and social capital scales were included in the contextual factors. Chronic disease self-efficacy is a process factor and the outcome factors included level of engagement with health care provider, level of adherence and reasons for non-adherence.

The sample was 91 women from two US cities who self-reported less than 100% adherence in the past three days. They were mostly African American, single, and unemployed. Race and employment were the two factors that had a significant association with a reason. African Americans and those employed were associated with wanting to avoid side effects and being away from home, respectively. Overall the most

frequent reason reported was simply forgot. The frequency of reasons reported did not consistently correspond with level of adherence. The findings from this study suggest that reasons for non-adherence are discrete; women taking ART in this sample provide a complex profile, and integrating a self-management framework for women can support appropriate and feasible intervention development for women taking ART.

Conclusion

The three papers presented on the following pages provide a scientific contribution to address the topic of this dissertation, *HIV Medication Adherence: Reasons for Missed Medication and Rethinking the Trajectory.* The three papers presented in this dissertation provide a lens in which to gain a better understanding of HIV medication adherence behavior using reasons for missed medications as the focus. Each of the three papers illuminate a facet of the scholarship surrounding HIV medication adherence and coalesces in order to present an enhanced picture of the dynamic nature of adherence. The final chapter of this dissertation will discuss the contributions, limitations and recommendations of these three papers, as well as provide suggestions for rethinking the trajectory of HIV adherence for nursing research.

Problems taking pills: Understanding HIV medication adherence from a new perspective

Key words: HIV; medication adherence; regimen; symptom experience; reasons for missed medications

Title

Problems taking pills: Understanding HIV medication adherence from a new perspective

Author
Jennifer G. Okonsky, RN MA, Doctoral Candidate
University of California, San Francisco
School of Nursing, Community Health Systems

Abstract

HIV medication adherence remains a challenge for people taking antiretroviral therapy (ART). In the last decade research in this area has proliferated, yet there is a need for novel research approaches that provide information on the development of successful medication adherence interventions. This study examined several key potential correlates of reasons for missed medication in a diverse sample of people living with HIV/AIDS (PLWHA) from nine cities in the US using an ordinal regression model. Examining the reasons for missed medication in relationship with regimen type, symptom experience, AIDS diagnosis, other health conditions, and social support offers a new approach. Problems taking pills, (a factor of five reasons) was significantly associated (p=.003) with use of a protease inhibitor (PI) regimen. A person taking a PI regimen is 1.7 odds of having more problems taking pills versus a non-PI based regimen. Symptom experience (OR: 3.8; 95% CI: 2.7, 5.2) and other health conditions (OR: 0.7; 95% CI: .45, .98) were found to be independently associated with problems taking pills. This new perspective may provide a framework for further conceptualizing new analyses that are related to enhancing adherence intervention research and development.

Introduction

Research exploring HIV medication adherence has proliferated in the last decade. Patterns, correlates, barriers and facilitators to adherence, and patient and regimen characteristics associated with non-adherence to antiretroviral therapy have been extensively examined (Ammassari et al., 2002; Barfod, Sorensen, Nielsen, Rodkjaer & Obel, 2006; Catz, Kelly, Bogart, Benotsch & McAuliffe, 2000; Chesney et al., 2000; Protopopescu et al., 2009; Remien et al., 2003; Sullivan et al., 2007). Since 1992, research has guided the development of several instruments on reasons for missed medications (Chensey et al.,2000; Muma et al., 1995; Murphy et al., 2004; Samet et al., 1992; Walsh et al., 2001) and select researchers have examined the association of reasons for missed medications with HIV medication adherence (Amico et al., 2007; Barfod et al., 2006; Kalichman, Catz & Ramachandran, 1999; Ferguson et al., 2002; Vyavaharkar et al., 2007; Walsh, Horne, Dalton, Burgess & Gazzard, 2001). Although, the existing research has reasons for missed medications as a common variable, a range of associations was explored using various reasons for missed medication instruments.

In 1999, Kalichman, Catz, and Ramachandran linked low education literacy in African American adults with decreased adherence in relation to confusion about medications, sleeping through a dose, and feeling depressed or overwhelmed. Catz, Kelly, Bogart, Benotsch, and McAuliffe (2000) reported that confusion about regimens, number of pills, appearance of pills, medication instructions, traveling to appointments, and questions around benefits of taking medications differed between adherent and nonadherent participants. Barfod et al. (2006) found no difference in reasons between adherent and

nonadherent participants. Ferguson et al. (2002) analyzed 25 patient reasons for non-adherence and the associations with race and gender and found that adherence was not different between racial and gender groups, but the reasons for missed medications were differentially endorsed across groups. Women were more likely to report forgetting to refill medications and not understanding how to take them while Caucasians were more likely than African Americans (AA) to report that medications were not convenient to take and AA did not take medications when they felt well. Walsh, Horne, Dalton, Burgess & Gazzard (2001) examined the prevalence of non-adherence to protease inhibitor (PI) based regimens and frequency of reasons. Eighteen reasons were placed into three factors: 1) low priority for taking medication, 2) negative experiences of HAART, and 3) unintentionally missing doses. Low priority for medication and unintentionally missing doses were independently associated with non-adherence. Amico et al. (2007) examined 14 common reasons (Chesney et al., 2000; Murphy et al., 2004; Walsh et al., 2001) for non-adherence and how gender, economic disparities, employment status, and feelings of dysphoria impacts adherence. Different adherence patterns emerged with women and individuals with moderate to severe depressive symptoms. Feeling sick and wanting to take a break from the medications were common in both women and the moderate to severe depressed groups. Adherence was not correlated with total number of reasons for missed medications. Vyavaharkar et al. (2007) focused on HIV women with depression. The study used two proxy variables to measure adherence: self-reported missed HIV medications and reasons for missed medications. The regression model used in the analysis was significant and accounted for 30% of the variability in reasons for missed medications. Coping by denial/avoidance and number of

children were positive predictors of reasons for missed medications while coping by managing HIV disease was a negative predictor.

Contextual variables including race, gender, employment, economic status, literacy, depression, and regimen have been explored to better understand the relationship between adherence and reasons for missed medications. Increased understanding of the associations between adherence, reasons for missed medication, and key correlates can offer critical information for adherence intervention development and strategies for improvement. The purpose of this study was to examine several key correlates of reasons for missed medication in a diverse sample of people living with HIV/AIDS (PLWHA) from nine cities in the United States using an ordinal regression model. Regimen type, symptom experience, AIDS diagnosis, other health conditions, and social support offer a common profile of PLWHA and complements the existing literature. Analyzing the reasons for missed medications in relationship with these correlates using an ordinal regression model offers a new perspective to understanding HIV medication adherence. The findings may support a framework for ongoing and extended analyses that can provide information for novel medication adherence intervention development and clinician strategies for improving adherence.

Methods

Design

This study, with approval from the Committee on the Protection of Human Subjects at the University of California, San Francisco, was a secondary analysis of quantitative data

obtained from a randomized controlled trial: The Efficacy of the HIV/AIDS Symptom Management Manual (Wantland et al., 2008). The parent study was designed to investigate the efficacy of a HIV/AIDS symptom management manual as compared to a basic nutrition manual on reducing symptom frequency and intensity. A repeated measures design was used and data was collected at three time points: baseline, one month (4-6 weeks), and two months (7- 12 weeks).

Participants

Participants were recruited from HIV community settings and clinics. Exclusion criteria included a diagnosis of dementia, inability to understand consent procedures, no symptoms within the past week, and prior experience with a self care manual.

Measures

Data

The data were collected between December 2005 and January 2007. Deidentified data were used in this analysis. Data were drawn from the Revised Adult AIDS Clinical Trials Group Reasons for Non-Adherence to Medications (ACTGrev) instrument and The Revised Sign and Symptom Checklist for Persons with HIV Disease (SSC-HIVrev). The demographic and illness background information extracted from the parent data set included age, gender, city, race, HIV medication, AIDS diagnosis, other health conditions, and social support.

Dependent variable

Revised ACTG Reasons for Non-Adherence to Medications (ACTGrev)

The ACTGrev Reasons for Non-Adherence to Medications revised instrument is a nine item self-report measure (Holzemer et al., 2006) of reasons for missing medication. Five items factor into problems taking pills and four items factor into forgetfulness. Problems taking pills is comprised of the following reasons: 1) wanted to avoid side effects, 2) felt sick or ill, 3) too many pills to take, 4) felt depressed/overwhelmed, and 5) problems taking pills at specified times. The forgetfulness factor reasons include: 1) too busy with other things, 2) away from home, 3) simply forgot, and 4) fell asleep/slept through dose time. The 4-point Likert ordinal scale allows participants to respond on the frequency of missing their medications with never, rarely, sometimes, or often.

Independent variables

Symptom experience

The Revised Sign and Symptom Checklist for Persons with HIV Disease (SSC-HIVrev).

The Revised Sign and Symptom checklist identifies both the common symptoms and the intensity of those symptoms experienced by people living with HIV in the previous 24 hours. The SSC-HIVrev has 72 items in three factors. Factor one consists of 45 HIV-related physical and psychological symptoms, (reliability estimates ranging from 0.76-0.91), factor two consists of 19 HIV-related clinical symptoms, and factor three consists of eight items related to gynecological symptoms for women. The participant marks mild, moderate, or severe to a specific symptom and if a participant does not have the symptom

it is left blank. Scoring is zero to three with zero for no symptom, one for mild, two for moderate, and three for severe.

Regimen, AIDS diagnosis, *Other health conditions, Social support*

Medication regimen was collected using a check off sheet that asked participants to indicate which HIV medications they are presently taking. AIDS diagnosis and other health conditions was a yes or no answer, and social support was measured by asking how one rates social support at the time, where one is very poor and ten is excellent.

Data Analysis

Data were analyzed using Stata version 10.0 (Stata Corporation, College Station, TX). The regression model used for ordinal dependent variables was the proportional odds model (POM). The POM is considered an extension of the logistic regression model for dichotomous dependent variables. Under the POM the assumption is that the odds ratio (OR) for being in a chosen category or higher compared to being in a lower category is the same regardless of which cut point is chosen. The model is not equivalent to first dichotomizing the outcome variable and then using logistic regression. However, it is more efficient because it makes use of the greater information available from the ordinal variable. The unique contribution of the POM is that the OR for a predictor is interpreted as a summary of the OR obtained from all possible cut points of the ordinal outcome. In an ordinal scale where one has four levels (1,2,3,4), three logits are modeled using the following cut points: 1 vs. 2,3,4; 1,2 vs. 3,4; and 1,2,3, vs. 4 (Scott, Goldberg, & Mayo, 1997). An OR greater than 1 indicates the predictor is associated with being “higher” on

the ordinal scale. This method assumes that the OR for being "higher" on the ordinal scale versus being "lower" on the ordinal scale is identical wherever the cut point is chosen. The ACTGrev instrument, which provided the outcome data, was scored with responses on a range from zero to three. The average score over each factor, problems taking pills and forgetfulness was taken. Minimally and fully adjusted models were run. A Wilcoxon rank sum test was used to examine the association of protease inhibitor (PI) regimen versus a non-PI regimen and the ACTGrev instrument. The SSC-HIVrev score was compiled from factors one (physical and psychological) and two (clinical symptoms). A continuous score average for symptom experience over all the responses was taken.

Results

Participants

The participants totaled 558, from nine cities in the United States. Seventy-five percent (n=416) reported taking HIV medications at baseline. The mean age of those taking HIV medications was 43.9, (SD of 9.1) and 29% (n=119) were females. Refer to Tables 1 and 2 for complete sample characteristics. Forty-four percent (n=183) were taking a protease inhibitor (PI) based regimen, 50% (n=208) had ever been told they have AIDS, and 65% (n=272) reported other health conditions. The top three conditions reported were depression, hypertension and Hepatitis C (26%, 22% and 11% respectively). Other conditions reported were TB, Hepatitis B, various cancers, herpes, and thyroid disease. The SSC-HIVrev had a mean intensity score of 0.65 (SD of 0.60), indicating less than mild symptom severity. For those on a PI based regimen, the five most frequent

symptoms were: fatigue, depression, difficulty concentrating, muscle aches, and fear/worries.

The association of PIs with a composite score of the overall ACTGrev instrument and the two factors, problems taking pills and forgetfulness was analyzed. Problems taking pills was associated with use of PIs ($p = .003$) and forgetfulness was not ($p = .229$). The following analyses were based on problems taking pills and persons on a PI based regimen.

Minimally and fully adjusted models were run (refer to Table 3). Time, age, gender, and race were not significant in the models. In the minimally adjusted model AIDS diagnosis (OR= 1.5; 95% CI: 1.1, 2.1) was associated with having more problems taking pills, but not in the fully adjusted model. Both the minimally and fully adjusted models resulted in an adjusted OR of 1.7 for PI based regimens and an adjusted OR of 3.8 for symptom experience. In this sample persons taking a PI based regimen had a 70% increase in problems taking pills (OR: 1.7; 95% 1.1, 2.4). An increase in symptom experience revealed PLWHA are approximately four times more likely to have problems taking pills (OR=3.8; 95% CI: 2.7, 5.2). Individuals with other health conditions were 30% less likely to have problems taking pills (OR=0.7; 95% CI: .45, .98).

Discussion

Understanding the associations of reasons for missing medications provides critical information that can support medication adherence intervention development. This study

used reasons for missed medications as a dependent variable, which is an alternative perspective when looking at HIV medication adherence. Although reasons for missed medications cannot be directly associated with level of adherence, this view may illuminate information regarding adherence patterns. Analyzing the relationship between reasons for missed medications and key correlates, coupled with existing research can alert HIV providers to a common profile in order to address areas of needed support for patients taking ART.

In this study a PI based regimen, symptom experience, and other health conditions are independent variables associated with reasons for missed medication, specifically problems taking pills (wanting to avoid side effects, felt sick or ill, too many pills to take, felt depressed/overwhelmed, and problems taking pills at specified times). These findings complement existing adherence research in terms of specific reasons and independent factors. Mannheimer et al. (2002), found people taking a non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen as compared to a protease inhibitor (PI) regimen were more likely to report 100% adherence. Maggiolo et al. (2005) and Trotta et al. (2003) also reported people taking NNRTI based regimens had better adherence than persons taking a PI based regimen. Wantland et al. (2008) found people taking a PI based regimen reported higher than expected symptoms. Other studies support the experience that more symptoms are associated with poor adherence (Ammassari et al., 2002; Heath et al., 2003). Copper, Gellaitry, Hankins, Fisher & Horne, (2009) found patients who experience persistent symptoms while on ART begin to doubt their continued need for treatment and respond by missing doses. It is important to note that

often clinicians and PLWHA identify symptoms as being focused on CD4 counts or those directly related to opportunistic infections. However, evidence provides that PLWHA experience symptoms not just directly related to CD4 counts and OIs but also depression, fatigue, fear and worries (Willard et al., 2010). This study also found that depression, fatigue, fear and worries, were in the top five most recorded symptoms. The value of these findings coupled with existing research, in terms of PI based regimens and symptom experience, highlights the need for providers to strategize around problems taking pills when discussing adherence with patients and for researchers when developing interventions.

The importance of exploring other health conditions as an independent variable of missed medications is highlighted due to HIV infection being considered a chronic condition. Living longer and prolonged ART puts PLWHA at an increased risk for developing other chronic health conditions. A study conducted by Ship, Wolff & Selik (1999) found that PLWHA aged 55 years and older have four times more chronic comorbid conditions than those less than 45 years of age. Sixty five percent of participants in this study have other health conditions and the recent International Association of Physicians in AIDS Care [IAPAC], (2010) survey documented that 64% of PLWHA have comorbid conditions. Coordinating the care of multiple health conditions and managing the actual or potential medication interactions poses considerable challenges. Although it is plausible that PLWHA managing other health conditions places them at a higher risk of decreased medication adherence, this study found that participants reporting other health conditions had less problems taking pills. Managing multiple health conditions can be challenging

and perhaps people with multiple conditions, including HIV/AIDS, receive additional assistance that mitigates problems taking pills. It is necessary that this finding be explored further. An understanding of how problems taking pills and other health conditions relate to one another is essential when researching HIV medication adherence.

Existing research describing the relationship between AIDS diagnosis and medication adherence is inconsistent. Schonnesson et al. (2007) found that adherence to ART was not significantly associated with AIDS diagnosis, while Samet et al. (1992) and Gao et al. (2000) found an AIDS diagnosis was independently associated with greater adherence. For the 208 persons in this sample that were told they had AIDS, they are 50% more likely to have problems taking pills (minimally adjusted model). More investigation is needed to understand how AIDS diagnosis is associated with reasons for missed medications and adherence.

Social support and the association with HIV medication adherence and non-adherence has been widely studied (Bader et al., 2006; Bodenlos et al., 2007; Catz et al., 2000; Gonzalez et al., 2004; Mostashari et al., 1998; Murphy, Roberts, Martin, Marelich, & Hoffman, 2000; Murphy, Marelich, Hoffman, & Steers, 2004; Power et al., 2003; Protopopescu et al., 2009; Remien et al., 2003; Roberts, 2002; Safren et al., 2001; Simoni, Frick, & Huang, 2006; Spire et al., 2002; Turner, 2002; Vyavaharkar et al, 2007). Social support as a predictor of adherence and the role it plays in coping strategies has been helpful in providing guidance for adherence intervention development. However, the connection between social support and reasons for missing medications has not been

clear. This study found no association between social support and reasons for missed medications. Critically viewing the role of social support from various angles and its association in a framework may offer individual strategies in adherence support.

Examining the reasons for missed medications, the role they play in medication adherence, and the relationship with regimen, symptom experience, other health conditions, social support, and AIDS diagnosis is an important component to consider in HIV medication adherence research. Although the existing research on reasons for missed medications is not consistent in terms of analysis, documented reasons, and selected variables, it is providing an impetus to conduct more extensive and innovative studies. The conceptualization of adherence is a complicated and dynamic phenomenon that requires creative research for the development of realistic interventions.

Limitations

This study was a secondary analysis that did not document a quantitative measure of adherence (percent of medications taken) or identify whether the participants were treatment experienced or treatment naïve. The independent variables selected were not presented in a theoretical framework in order to guide the translation of the results. Although the ACTGrev is unique in its factor breakdown and provides common reasons, it is not comprehensive. Social support was measured on a scale of one to ten which presents a one-dimensional perspective. The exclusion criteria regarding symptoms excluded persons who were symptom free in the last week, which may potentially have implications for the generalizability of the findings.

Conclusion

This study offers a foundation to further explore the connection between reasons for missed medications, specifically problems taking pills, with those on a PI based regimen. Further, a reconceptualization of the analyses presents a new perspective on examining reasons for missed medications and the relationship with regimen, symptom experience, AIDS diagnosis, other health conditions, and social support. Moving forward using these modeled analyses requires further prudent research including a quantitative measure of adherence and a framework of factors that provide a profile to assist providers to develop a tailored plan of care specific for someone taking a PI based regimen. The potential clinical implications of using reasons for missed medications along with a quantitative measure of adherence, as a dependent variable, may provide innovative guidance for HIV medication adherence interventions.

References

Amico, R., Konkle-Parker, D., Cornman, H., Barta, W., Ferrer, R., Norton., et al. (2007). Reasons for ART non-adherence in the Deep South: Adherence needs of a sampoe o fHIV-positive patients in Mississippi. *AIDS Care, 19*(10), 1210-1218.

Ammassari, A., Trotta, M. P., Murri, R., Castelli, F., Narciso, P., Noto, P., et al. (2002). Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *Journal of Acquired Immune Deficiency Syndromes, 31 Suppl 3*, S123-127.

Bader, A., Kremer, H., Erlich-Trungenberger, I., Rojas, R., Lohmann, M., Deobald, O., et al. (2006). An adherence typology: coping, quality of life, and physical symptoms of people living with HIV/AIDS and their adherence to antiretroviral treatment. *Medical Science Monitor, 12*(12), CR493-500.

Bakken, S., Holzemer, W. L., Brown, M. A., Powell-Cope, G. M., Turner, J. G., Inouye, J., et al. (2000). Relationships between perception of engagement with health care provider and demographic characteristics, health status, and adherence to therapeutic regimen in persons with HIV/AIDS. *AIDS Patient Care STDS, 14*(4), 189-197.

Barfod, T. S., Sorensen, H. T., Nielsen, H., Rodkjaer, L., & Obel, N. (2006). 'Simply forgot' is the most frequently stated reason for missed doses of HAART irrespective of degree of adherence. *HIV Medicine, 7*(5), 285-290.

Bodenlos, J. S., Grothe, K. B., Whitehead, D., Konkle-Parker, D. J., Jones, G. N., & Brantley, P. J. (2007). Attitudes toward health care providers and appointment attendance in HIV/AIDS patients. *Journal of the Association of Nurses in AIDS Care, 18*(3), 65-73.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology, 19*(2), 124-133.

Chesney, M. A., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J., Zwickl, B., et al. (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care, 12*(3), 255-266.

Cooper, V., Gellaitry, G., Hankins, M., Fisher, M., & Horne, R. (2009). The influence of symptom experiences and attributions on adherence to highly active anti-retroviral therapy (HAART): a six-month prospective, follow-up study. *AIDS Care, 21*(4), 520-528.

Ferguson, T.F., Stewart.K.E., Funkhouser, E., Tolson, J., Westfall, A.O., & Saag, M.S. (2002). Patient-perceived barriers to antiretroviral adherence: Associations with race. *AIDS Care, 14*(5), 607-617.

Gao, X., Nau, D. P., Rosenbluth, S. A., Scott, V., & Woodward, C. (2000). The relationship of disease severity, health beliefs and medication adherence among HIV patients. *AIDS Care, 12*(4), 387-398.

Gonzalez, J. S., Penedo, F. J., Antoni, M. H., Duran, R. E., McPherson-Baker, S., Ironson, G., et al. (2004). Social support, positive states of mind, and HIV treatment adherence in men and women living with HIV/AIDS. *Health Psychology, 23*(4), 413-418.

Heath, K. V., Montaner, J. S., Bondy, G., Singer, J., O'Shaughnessy, M. V., & Hogg, R. S. (2003). Emerging drug toxicities of highly active antiretroviral therapy for human immunodeficiency virus (HIV) infection. *Current Drug Targets, 4*(1), 13-22.

Holzemer, W. L., Bakken, S., Portillo, C. J., Grimes, R., Welch, J., Wantland, D., et al. (2006). Testing a nurse-tailored HIV medication adherence intervention. *Nursing Research, 55*(3), 189-197.

International Association of Physicians in AIDS Care [IAPAC]. (2010, July 10). Global HIV/AIDS survey by IAPAC reveals critical gap in patient-physician conversations. Retrieved from http://www.eurekalert.org/pub_releases/2010-07/cw-ghs072010.php.

Kalichman, S.C., Catz, S., & Ramachandran, B. S.(1999). Barriers to HIV/AIDS treatment and treatment adherence among African-American adults with disadvantaged education. *Journal of the National Medical Association, 91*(8), 439-446.

Maggiolo, F., Ravasio, L., Ripamonti, D., Gregis, G., Quinzan, G., Arici, C., et al. (2005). Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. *Clinical Infectious Diseases, 40*(1), 158-163.

Mannheimer, S., Friedland, G. H., Matts, J., Chold, C., & Chesney,M. (2002).The consistency of adhernce to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus infected persons in clinical trials. *Clinical Infectious Diseases, 34,* 1115-1121.

Mostashari, F., Riley, E., Selwyn, P. A., & Altice, F. L. (1998). Acceptance and adherence with antiretroviral therapy among HIV-infected women in a correctional facility. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 18*(4), 341-348.

Muma, R.D., Ross, M.W., Parcell, G.S., & Pollard, R. B. (1995). Zidovudine adherence among individuals with HIV infection. *AIDS Care,* 7(4), 439-447.

Murphy, D. A., Marelich, W. D., Hoffman, D., & Steers, W. N. (2004). Predictors of antiretroviral adherence. *AIDS Care, 16*(4), 471-484.

Murphy, D. A., Roberts, K. J., Martin, D. J., Marelich, W., & Hoffman, D. (2000). Barriers to antiretroviral adherence among HIV-infected adults. *AIDS Patient Care STDS, 14*(1), 47-58.

Power, R., Koopman, C., Volk, J., Israelski, D. M., Stone, L., Chesney, M. A., et al. (2003). Social support, substance use, and denial in relationship to antiretroviral treatment adherence among HIV-infected persons. *AIDS Patient Care STDS, 17*(5), 245-252.

Protopopescu, C., Raffi, F., Roux, P., Reynes, J., Dellamonica, P., Spire, B., et al. (2009). Factors associated with non-adherence to long-term highly active antiretroviral therapy: a 10 year follow-up analysis with correction for the bias induced by missing data. *Journal of Antimicrobial Chemotherapy., 64*(3), 599-606.

Remien, R. H., Hirky, A. E., Johnson, M. O., Weinhardt, L. S., Whittier, D., & Le, G. M. (2003). Adherence to medication treatment: a qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities. *AIDS and Behavior, 7*(1), 61-72.

Roberts, K. J. (2002). Physician-patient relationships, patient satisfaction, and antiretroviral medication Adherence among HIV-infected adults attending a public health clinic. *AIDS Patient Care STDS, 16*(1), 43-50.

Safren, S. A., Otto, M. W., Worth, J. L., Salomon, E., Johnson, W., Mayer, K., et al. (2001). Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behavior Research Therapy, 39*(10), 1151-1162.

Safren, S. A., Otto, M. W., Worth, J. L., Salomon, E., Johnson, W., Mayer, K., et al. (2001). Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behavior Research Therapy, 39*(10), 1151-1162.

Samet, J. H., Libman, H., Steger, K. A., Dhawan, R. K., Chen, J., Shevitz, A. H., et al. (1992). Compliance with zidovudine therapy in patients infected with human immunodeficiency virus, type 1: a cross-sectional study in a municipal hospital clinic. *American Journal of Medicine, 92*(5), 495-502.

Schonnesson, L.N., Williams, M.L., Ross, M.W., Diamond, P.M., & Keel, B. (2007). Three types of adherence to HIV antiretroviral therapy and their association with AIDS diagnosis, medication side effects, beliefs about antiretroviral therapy, and beliefs about HIV disease. *International Journal of STD & AIDS, 18*, 369-373.

Scott, S. C., Goldberg, M. S., & Mayo, N. E. (1997). Statistical assessment of ordinal outcomes in comparative studies. *J Clin Epidemiol, 50*(1), 45-55.

Ship, J. A., Wolff, A., & Selik, R.M. (1991). Epidemiology of acquired immune deficienty syndrome in persons aged 50 years of older. *Journal of Acquired Immune Deficiency Syndromes,* (4), 84-88.

Simoni, J. M., Frick, P. A., & Huang, B. (2006). A longitudinal evaluation of a social support model of medication adherence among HIV-positive men and women on antiretroviral therapy. *Health Psychology, 25*(1), 74-81.

Spire, B., Duran, S., Souville, M., Leport, C., Raffi, F., & Moatti, J.-P. (2002). Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. *Social Science & Medicine, 54*(10), 1481-1496.

Sullivan, P. S., Campsmith, M. L., Nakamura, G. V., Begley, E. B., Schulden, J., & Nakashima, A. K. (2007). Patient and regimen characteristics associated with self-reported nonadherence to antiretroviral therapy. *PLoS One, 2*(6), e552.

Trotta, M. P., Ammassari, A., Cozzi-Lepri, A., Zaccarelli, M., Castelli, F., Narciso, P., … Antinori, A. (2003). Adherence to highly active antiretroviral therapy is better in patients receiving non-nucleoside reverse transcriptase inhibitor-containing regimens than in those receiving protease inhibitor-containing regimens. *Aids, 17*(7), 1099-1102.

Turner, B. J. (2002). Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. *Journal of Infectious Diseases, 185 Suppl 2*, S143-151.

Vyavaharkar, M., Moneyham, L., Tavakoli, A., Phillips, K. D., Murdaugh, C., Jackson, K., & Meding, G. (2007). Social support, coping, and medication adherence among HIV-positive women with depression living in rural areas of the Southeastern United States. *AIDS Patient Care and STDs, 21*(9), 667-680.

Walsh, J. C., Horne, R., Dalton, M., Burgess, A. P., & Gazzard, B. G. (2001). Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care, 13*(6), 709-720.

Wantland D.J., Holzemer W.L., Moezzi S., Willard S.S., Arudo, J., Kirksey, K.K., … Huang, E. (2008). A randomized controlled trial testing the efficacy of an HIV/AIDS symptom management manual. *Journal of Pain and Symptom Management, 36* (3), 235-46.

Willard, S., Holzemer, W. L., Wantland, D. J., Cuca, Y. P., Kirksey, K. M., Portillo, C. J., … Lindgren T. (2009). Does "asymptomatic" mean without symptoms for those living with HIV infection? *AIDS Care, 21*(3), 322-328.

Acknowledgements

This work was supported in part by NIH Training Grant T32 NR007081, funded by the National Institute of Nursing Research and in part by NIH Training Grant T32 RR023259.

The author would also like to acknowledge the following: Dr Carmen Portillo, Dr William Holzemer, Dr Mallory Johnson, Dr Carol Dawson-Rose; The UCSF International Nursing Network for HIV/AIDS Research and Eric Vittinghoff, UCSF, Epidemiology and Biostatistics Department.

Table 1: Sample characteristics of HIV+ Persons in 9 cities in the US

	Baseline (*n*=558)	**Time 1 (*n*=421)**	**Time 2 (*n*=340)**
	n (%) or Mean ±SD		
Study site in the US			
Boston, MA	69 (12)	60 (14)	53 (16)
San Francisco, CA	86 (15)	64 (15)	60 (18)
San Diego, CA	21 (4)	18 (4)	17 (5)
Chicago ,IL	16 (3)	10 (2)	10 (3)
Philadelphia, PA	107 (19)	77 (18)	73 (21)
Salt Lake City, UT	69 (12)	45 (11)	31 (9)
Harlingen, TX	61 (11)	37 (9)	28 (8)
Corpus Christi, TX	56 (10)	47 (11)	38 (11)
Houston, TX	73 (13)	63 (15)	30 (9)
Gender			
Female	167 (30)	125 (30)	97 (29)
Male	378 (68)	286 (68)	234 (69)
Transgender	13 (2)	10 (2)	9 (2)
Age	43.9±9.01	44.7±8.74	45±8.81

Table 2: Sample characteristics of persons taking HIV medications

	Baseline (*n*=416)	**Time 1 (*n*=324)**	**Time 2 (*n*=263)**
	n (%) or Mean ±SD		
Age	43.9±9.1	44.6±8.86	45±9.06
Race			
African American/Black	163 (39)	123 (38)	102 (39)
Hispanic/Latino	100 (24)	73 (23)	51 (20)
White/Anglo	126 (30)	108 (33)	93 (35)
Other *(Asian/Pacific Islander/Native American/Indian)*	27 (6)	20 (6)	17 (6)
Gender			
Female	119 (29)	94 (29)	71 (27)
Male	287 (69)	222 (69)	185 (70)
Transgender	10 (2)	8 (2)	7 (3)
On PI based regimen	183 (44)	69 (21)	39 (15)

Table 3: Proportional Odds Model with dependent variable: Problems taking pills

Independent variable	**Minimally adjusted** ***(Age, gender and race adjusted: Not significant)***		**Fully adjusted**	
Measure of association	**Adjusted OR (95% CI)**	**p**	**Adjusted OR (95% CI)**	**p**
PI based regimen	1.7 (1.2, 2.4)	.00	1.7 (1.1, 2.4)	.01
Symptom experience	3.8 (2.8, 5.2)	.00	3.8 (2.7, 5.2)	.00
Other health conditions	0.8 (.56, 1.2)	.24	0.7 (.45, .98)	.04
AIDS diagnosis	1.5 (1.1, 2.1)	.02	1.4 (.96, 1.9)	.08
Social support	1.1 (1.0, 1.2)	.03	1.0 (.97, 1.1)	.27

Not *Just* Simply Forgetting: Appreciating Reasons for Missed Medication in Women by Adherence Level and Regimen

Title: Not *Just* Simply Forgetting: Appreciating Reasons for Missed Medication in Women by Adherence Level and Regimen

Abstract

HIV adherence research has consistently reported that forgetfulness is a leading reason people are nonadherent. The purpose of this study was to examine and gain an appreciation of the reasons why HIV infected women taking antiretroviral therapy in two cites in the US are missing their HIV medications, and how the results can influence a new trajectory of HIV ART non-adherence research. In this sample, women were 2.2 times more likely to document reasons pertaining to forgetfulness than problems taking pills (OR= 2.2, 95% CI: 1.63, 2.94, $p<0.001$). There was a difference between the adherent and nonadherent groups in reasons for missed medications given overall, ($p<.000$, 95%CI -3.82, -2.03), but no difference between those on a PI based versus a non-PI based regimen ($p=.35$, 95%CI -0.492, 1.389). A patient-centered approach that reviews type of reason, frequency of reasons and type of non-adherence (intentional vs. unintentional) can support development of novel interventions.

Key words: HIV; non-adherence; reasons; women; patient-centered

Introduction

In 2009, nearly twenty-five percent of newly diagnosed cases of HIV in the United States were women and most of those infected are minorities and of low socioeconomic status (Centers for Disease Control and Prevention, 2011). Women living with HIV and AIDS (WLHA) taking antiretroviral therapy (ART) are more likely to have lower rates of medication adherence when compared to men (Arnsten, et al., 2002; Lopez, Jones, Villar-Loubet, Arheart & Weiss, 2010; McNabb et al., 2001) and consequently adherence to ART remains a critical concern in this population. Decades of research has identified and described predictors of non-adherence and strategies for people to reach optimal adherence levels, but adherence continues to be a challenge for most people living with HIV and AIDS (PLWHA). While this research has provided guidance for reaching and maintaining optimal adherence levels, as HIV has become a chronic condition, with many competing self-management tasks, continuing to add to this body of literature is necessary. To ensure adherence, nurses caring for WLHA need novel evidence-based strategies that can accommodate the unique experience of the context of women's lives.

Adherence to Antiretroviral Therapy: Reasons literature

In 1992 Samet et al. recorded PLWHA taking monotherapy documented 'simply forgetting' as the main reason for missing their HIV medications, and forgetting has consistently been documented in the top five reasons for non-adherence (Heckman, Catz, Heckman, Miller & Kalichman, 2004; Hill, Kendall, & Fernandez, 2003; Kalichman, Catz & Ramachandran, 1999; Sullivan, Campsmith, Nakamura, Begley, Schulden & Nakashima, 2007). Research exploring the reasons for non-adherence and degree of

adherence has expanded. Catz et al. (2000) found differences between adherent and nonadherent persons regarding confusion about regimens, number and appearance of pills, instructions, and benefits of taking medications. Kalichman et al. (2001) explored adherent vs. nonadherent women (missed at least one dose in the past week) and compared the groups on HIV treatment knowledge, intentions to adhere, and self-efficacy for HIV treatment adherence. Nonadherent women demonstrated less intention to adhere to medication and less HIV treatment self-efficacy than those who were classified as adherent. Interestingly, improvements in adherence in women did not result from the implementation of adherence enhancement strategies such as timers, beepers, pill boxes, and reminder notes. Ferguson et al. (2002) examined 25 reasons and found that women were more likely to report forgetting to refill medications and did not understand how to take the medications compared to men. Barfod, Sorensen, Nielsen, Rodkjaier & Obel (2006) examined patients' self-reported reasons for missing doses of ART in 840 Danish adults (79% male) living with HIV. They compared reasons between those participants classified as low adherers (missing a dose within the preceding four days) and high adherers. "Simply forgot" was the still the most frequently stated reason, regardless of degree of adherence.

Research specifically focused on women and ART adherence is continuing to grow and expand not only in regard to reasons but also predictors. Lazo et al. (2007) examined patterns and predictors of change in adherence to ART over a 5-year period. Among the factors associated with decreasing adherence in women were a history of AIDS and a PI based regimen. Amico et al. (2007) recruited 72 PLWHA from Mississippi and found different adherence patterns among women and individuals with

moderate to severe depression. Adherence was not correlated with total number of reasons for missed medications. Feeling sick and wanting to take a break from the medications were common in both groups. Vyavaharkar et al. (2007) demonstrated that coping by denial/avoidance and numbers of children were positive predictors of reporting more reasons for missed medications in a cohort of 224 women with depression. Despite the many efforts to integrate reminder devices and strategies into a PLWHA's daily routine, forgetting currently remains the most frequently stated reason for non-adherence (Gay et al, 2011; Kyser et al., 2011). A recent systemic review by Saberi and Johnson (2011) found that the sole use of technology to remind patients to take ART was not the most effective method. The totality of this evidence suggests there may be a need for new adherence strategies that are more dynamic and can easily respond to an individual's unique situation including ART regimen, treatment for other non-AIDS defining complications, and other contextual factors.

Patient-Centered Adherence/Types of Non-adherence

Identifying reasons for non-adherence is just one dimension of adherence work. Simply charting 'forgetfulness' is no longer sufficient, and asking about reminder strategies is not enough to improve the outcomes for women living with HIV and AIDS. Appreciating the reasons for non-adherence and understanding the type of non-adherence by exploring the reasons within the individuals context (integrating a patient-centered approach), can be the catalyst for change, the coming back to the basics, that ART adherence needs. Although patient centeredness, patient-centered care approaches can be ambiguous and defined in a variety of ways (Laws, Epstein, Lee, Rogers, Beach & Wilson, 2011), keeping true to the original description by Balint (1969) "…the patient, in

fact, needs to be understood as a unique human-being" (p.1) allows for an individual's unique situation to be explored. Wilson (2010) in his article on improving treatment adherence highlights selected studies looking at adherence prediction, rates and interventions. Adherence usually declines after the first few months, (Wilson, 2010a; Wilson, 2010b) there is difficulty predicting which patients will have adherence problems, efficacious interventions for improving adherence are not simple, and the magnitude of improvement in interventions is often small (Simoni, Amico, Smith, & Nelson, 2010). Wilson (2010) recognizes that approaches such as patient-centered care, adult learning theory and motivational interviewing have been gaining in managing adherence in PLWHA. He also addresses that there is a type of non-adherence, voluntary and involuntary. He states:

> Non-adherence may be voluntary (i.e., patient may choose not to use their medication as prescribed), or it may be involuntary (i.e., patients may wish to use their medication as prescribed, but forget or are otherwise prevented from doing so). Obtaining a thorough history is essential to understand the underlying causes of adherence problems. Conversational techniques such as reflective listening, understanding ambivalence, and assessing patient understanding can help patients to find their own reasons for remaining adherent to antiretroviral therapy. (p. 53).

Roberts and Mann (2003) also engage in exploring types of non-adherence. They explore the idea of intentional versus unintentional non-adherence. Intentional non-adherence refers to the deliberate aim not to take medications, and it occurs when patients who are knowledgeable about the medications choose not to adhere. They demonstrate the concepts of intentional and unintentional non-adherence through a qualitative study. They

studied 20 women between the ages of 25 and 54 living with HIV in the US, and collected women's own perceptions in diary format to better understand why these women intentionally fail to adhere to their ART. They highlight that as of 2003 no research has focused on intentional non-adherence to ART. Their study focused on women who provided insight into the world of intentional non-adherence. Roberts and Mann (2003) underscore the distinction between types of non-adherence (voluntary/involuntary vs. intentional/unintentional). Voluntary and involuntary can be descriptors of non-adherence, but the analytic distinction in terms of non-adherence is not the same.

> The analytic distinction between voluntary and involuntary non-adherence is an important one; some forms of non-adherence such as simply forgetting to take a pill (when one knows how to take the medication) are not easily recognizable as either voluntary or involuntary non-adherence. (Roberts and Mann, 2003, p. 554).

Roberts and Mann (2003) call attention to the fact that if interventions are to improve adherence, they must address both intentional and unintentional non-adherence. Research specifically looking at intentional and unintentional non-adherence has been studied in patients with asthma, lupus, hypertension, breast cancer, and chronic disease (Atkins & Fallowfield, 2006; Daleboudt, Broadbent, McQueen & Kaptein, 2010; Lehane & McCarthey, 2007; Lowry, Dudley, Oddone & Bosworkth, 2005; Wroe, 2002) and has also been represented in HIV, although scarce (Mo & Mak, 2009; Norton et al., 2010; Wroe & Thomas, 2003). Understanding intentional and unintentional non-adherence supports the notion of appreciating reasons for missed medication using the patient-centered approach.

Appreciating the reasons for non-adherence in PLWHA (understanding the type of non-adherence) can facilitate a more responsive patient-centered care approach. A level of appreciation can illuminate the complexities in our patients' treatment that may easily have been concealed. Allowing for an individuals' appreciation might just possibly be a tipping point for non-adherence by enabling an honest discussion between provider and patient on improving medication adherence, given the patient's unique situation. A recent study of adherence by Yard, Huh, King and Simoni (2011) examined patient level characteristics, inclusive of mental health, sociodemographic and interpersonal factors as moderators of two ART adherence strategies (peer support and pager reminders) in 224 men and women. It provides us with a lens highlighting the need to be mindful of synthesizing adherence literature, incorporating lessons learned, and understanding the needs of the individual patients. Placing patients into a subgroup or box of non-adherence predictors can potentially disengage and ignore the individual. Identifying a common profile is a starting point, and then gaining an appreciation for the individuals' needs and barriers can support people taking ART to adhere and stagnate the antiretroviral resistant epidemic.

There are a limited number of studies describing the reasons women living with HIV and AIDS (WLHA) miss taking their medications. The purpose of this study was to examine and gain an appreciation of the reasons why WLHA taking ART in Cleveland, OH and the San Francisco Bay Area of California are missing their HIV medications, and how the results can influence a new trajectory of HIV ART non-adherence research.

Methods

Participants and Procedure

A cross-sectional, descriptive study was conducted from October 2010 through March 2011. Adult women aged 18 years or older, confirmed HIV-positive serostatus, able to provide informed consent, English speaking, biologically female and able to self administer the questionnaire packet were eligible for the study. Recruitment of participants was done using flyers in Cleveland, Ohio, San Francisco and Oakland, California at medical clinics and community support organizations. University Hospitals, Case Medical Center and University of California San Francisco (UCSF) Institutional Review Boards approved the study protocol. All participants provided written informed consent. The questionnaire packet was self-administered and took participants 45-60 minutes to complete; participants were paid for their participation. The main study protocol focused on data collection to develop and validate a measure of self-management for women living with HIV and AIDS (Webel et al., 2011). This sub study on HIV adherence focused on reasons for missed medication in regard to adherence level (adherers versus nonadherers) and medication regimen.

Measures

Demographic, clinical characteristics and instruments

The self-administered questionnaire packet included demographic and clinical background items. Basic demographics included age, race, children, marital status, education level, annual income, housing, and insurance. Self-report included year

diagnosed with HIV, antiretroviral status, HIV medications, AIDS diagnosis, viral load, CD4+ T cell count and co-morbidities. Chart abstraction was completed at the Ohio clinic sites for viral load, CD4+ T cell count and year diagnosed with HIV. The scales and instruments inquired about pregnancy history, access to care, social capital, chronic disease self-efficacy, health care provider engagement, self-management, visual analog self-report adherence scale, AIDS Clinical Trials Group Revised (ACTGrev) reasons for missed medications, quality of life and stigma.

Reasons, Adherence level and Regimen

The ACTGrev Reasons for Missing Medications revised instrument (Holzemer et al., 2006) was used to capture reasons for missed medication in the past month. This nine-item, self-report measure uses a four point Likert ordinal scale that allows participants to respond on the frequency of missing their medications with never, rarely, sometimes or often. The first five items cluster into one factor "problems taking pills" and include: (1) wanted to avoid side effects, (2) felt sick or ill, (3) too many pills to take, (4) felt depressed/overwhelmed and (5) problems taking pills at specified times. The other four items cluster into the second factor "forgetfulness" and include: (1) too busy with other things, (2) away from home, (3) simply forgot, and (4) fell asleep/slept through the dose. The Cronbach's α reliability coefficient for this study was 0.93, and in previous studies it has ranged from .85 to .89 (Gay et al., 2011, Holzemer et al., 2006).

Self-reported adherence was measured on a visual analogue scale based on one's adherence level over three days. The scale is based on Walsh, Mandalia, & Gazzard (2002) 30-day adherence assessment. Participants marked their level of adherence with a 'X' on the line indicating zero to 100 percent in the last three days. If a participant

indicated a 'X' at 100% they were defined as adherent, and non-adherence was anything less than 100%. Over-reporting is a concern with self-reported measures which is why the authors choose a conservative cut off of anything less than 100% as nonadherent. Participants indicated from a chart listing 32 FDA approved HIV medications which ones they were currently taking. Regimen data was categorized into a protease inhibitor (PI) based regimen and a non-PI based regimen.

Analysis

We conducted our analysis with STATA version 11.0 (Stata corporation, College Station, TX). We calculated descriptive statistics to summarize demographic and clinical characteristics; and performed chi-square and t-tests to determine differences between the adherence level groups (adherent vs. nonadherent) and regimen (PI based vs. non-PI based) groups. The data from the ACTGrev instrument was dichotomized into persons who reported *never* missing their medication for that reasons and those who *ever* missed (included rarely, sometimes, and often) for that reason. A ranking was calculated on the percent of persons documenting ever missing their medication for each of the nine reasons, by adherence level and regimen. Additionally, chi-square tests were performed for each reason by adherence level and regimen. Rankings and chi-square testing were also completed with the following subgroups: (1) PI and adherence level, and (2) Non-PI and adherence level. We also conducted multi-level regression analysis to determine the overall difference between adherence level groups in reasons given and between regimen groups. An overall main effect with grouping reasons into the factors (problems taking

pills and forgetfulness) and an interaction between regimen group and factors (problems taking pills and forgetfulness) was analyzed.

Results

Participants

The sample size was 266 women, 131 women from the Cleveland site and 135 from the San Francisco Bay Area site. The mean age was 46 (SD: 9.3, range 22-71). No statistical differences were found between the sites. The number of participants in this study actively taking antiretroviral therapy (ART) totaled 206 (77%), with a mean age of 47 (SD: 9.2). One hundred and twenty-nine participants were African-American (64%). Our study focused on the 206 women actively taking ART. Thirty percent had less than a high school education, 59% single, 88% had children, 22% were working, 46% were ever told they had AIDS and there was a mean self-reported adherence level of 87%. Fifty-six percent of the women (n=115) documented 100% adherence in the last three days and 48% of the women in the sample (n=99) were taking a PI regimen. The median CD+ T cell counts for the adherent and nonadherent groups were 515 cells/mm^3 (IQR: 266-798) and 487 cells/mm^3 (244-714). Viral load (VL) was available for 66% of the sample and both the nonadherent and PI based regimen groups had a greater percentage of women with detectable viral loads (33%). The women on a PI regimen had lower CD4+ T cell counts, higher and more detectable viral loads, and a greater percentage of ever being told they had an AIDS diagnosis. Refer to Table 1 for complete demographic and clinical characteristics. The statistically significant differences noted between the groups was African American race and regimen (p=.001), self-reported adherence between the

adherent and nonadherent groups (p<.001) and self-reported adherence and regimen (p=.010) (not noted in the table).

Reasons for Missed Medications

'Simply forgot' was the dominant reason for missing medications in both the adherent and nonadherent groups. 'Away from home' and 'fell asleep' were the second and third most frequent reasons for missed medications in the adherent group, and 'problems taking pills at a specified time' and 'too busy with other things' ranked second and third in the nonadherent group. 'Wanted to avoid side effects' was the least frequent reason for missed medication in both groups. For each reason, a statistically significant difference was found between the adherent and nonadherent groups (Refer to Figure 1). Additionally, among those in the adherent group, 9% reported all nine reasons for *ever* missing a medication compared to 25% of the nonadherent group whom listed all nine.

In comparing reasons for missed medication by ART regimen, the top four reasons for having missed medication in the PI and non-PI groups differed. Among those in the PI based group, 'wanted to avoid side effects', 'too many pills to take', 'too busy with other things' and 'felt sick' were the four most frequent reasons, (three of these fall into the *Problems taking pills* factor). For those in the non-PI group, the most frequent reasons given for missing medications included 'being away from home', 'problems taking pills at specified times', 'fell asleep' and 'forgot', (three of these fall into the *Forgetfulness* factor). We did not find a significant difference between the reasons given between the two regimen groups (See Figure 2).

In the two sub group analyses, (1) PI based regimen and adherence level, and (2) non-PI based regimen and adherence level, a significant difference was found between the groups for each reason. 'Simply forgot' was the top ranked reason in the PI based regimen (n=99) among the adherers (n=50) and nonadherers (n=49). The top three reasons for both the adherers and nonadherers fell in the *Forgetfulness* factor. For those participants in the non-PI based group (n=107), the adherers (n=65) and nonadherers (n=42) had the same top five reasons for missing medication, with the most common being 'simply forgot' and the last ranked being 'wanted to avoid side effects'. Refer to Figure 3 and 4.

Using multi-level logistic regression analysis, we found a difference between the factors reported (Problems taking pills vs. Forgetfulness). On the whole, in this sample, women were 2.2 times more likely to document the reasons falling under the Forgetfulness factor than the reasons falling under the Problems taking pills factor (OR= 2.2, 95% CI: 1.63, 2.94, $p<0.001$). There was also a difference between the adherent and nonadherent groups in reasons for missed medications given overall, ($p<.000$, 95%CI -3.82, -2.03), but we did not find a difference between those on a PI based versus a non-PI based regimen across all reasons given for missed medication overall ($p=.35$, 95%CI -0.492, 1.389). When testing for an interaction between regimen group (PI vs. non-PI) and factors (Problems taking pills and Forgetfulness), we did not find a statistically significant difference (OR= 1.71, 95% CI: 0.624,4.68, $p=0.296$).

Discussion

HIV medication adherence research continues to focus on identifying determinants of adherence and predictors of non-adherence, as well as evidence supporting successful medication adherence interventions. However, not all PLWHA taking ART will be able to enroll in an experimental intervention or keep weekly or monthly appointments to complete an adherence intervention. Researchers and clinicians are highlighting the need for enhanced communication strategies and patient-centered approaches to improve ART adherence management (Rochon et al., 2011; Saha, Beach, & Cooper, 2008; Wilson, 2010). Appreciating and acknowledging individuals' reasons for missed medication can support the patient-centered approach for optimal medication adherence. As women continue to struggle with managing not only HIV/AIDS but additional chronic diseases, (Phillips, Neaton , & Lundgren 2008) the importance of appreciating the reasons for non-adherence can assist in overcoming barriers to ART adherence. The appreciation of how reasons for missed medications fits into the patient-centered approach provides the stepping stone for translational research to enter the health care providers enviornment.

In this sample with substantial representation of single, African American women with children, the mean adherence level was 87%, and participants were 2.2 times more likely to document reasons pertaining to forgetfulness than problems taking pill reasons. Fifty-six percent of the women in the sample self-reported 100% adherence for the past three days; and this finding is similar to a recent meta analysis (Ortego et al., 2011) of 84 observational studies in 20 countries on ART adherence which reported the mean proportion of adherence world wide is 62%.

Research has consistently demonstrated that forgetfulness is the leading reason people are nonadherent (Gay et al., 2011; Kyser et al., 2011). Our study supports this finding in an all-female sample. However, it is important to note that an overall difference was found in the type of reasons given between the adherent group (56% of the sample) and the nonadherent group. This can alert providers that type of reason can impact adherence level. For nurses that are actively discussing adherence with patients, a patient-centered approach that reviews type of reason, frequency of reasons and type of non-adherence (intentional vs. unintentional) can help elicit an individualized profile of non-adherence. In 2006, Barford et al. hypothesized that reasons for missed medications are different between adherers and nonadherers, and that forgetfulness is not as prominent in nonadherers, and may explain why reminder devices are not as effective for those who are nonadherers (Mannhiemer et al., 2006). And although both the Barfod study and our study both found simply forgot as the number one ranked reason irrespective of adherence level, we also found that the overall reasons for missed medications between adherers and nonadherers differed as did the frequency of reasons between these two groups. This evidence suggests that it is not *just* about simply forgetting, but about appreciating the reasons for non-adherence. Our finding provides insight that nonadherers may have a complex profile that requires a careful, individualized assessment.

Women in this sample taking a PI-based regimen reported reasons falling under problems taking pills factor more often than those on a non-PI based regimen. Okonsky, (2011) also described the reasons for missed medication among 416 PLWHA taking ART using the ACTGrev instrument. In her study with 44% on a PI based regimen, (29%

female), the problems taking pills factor was associated with the PI regimen and the forgetfulness factor was not. Additionally, PI based regimens have not only been shown to have lower level of adherence but also decreases in adherence have been documented over time (Lazo et al., 2007, Mannheimer, Friedland, Matts, Child, & Chesney, 2002). In our study, we documented women on a PI based regimen had a mean adherence level of 79% compared to 91% for women on a non-PI based regimen.

Walsh, Horne, Dalton, Burgess & Gazzard (2001) defined common reasons and frequency of reasons for nonadherent persons taking a PI based regimen. Those with lower adherence gave more reasons. Our study had similar findings: those grouped as nonadherent had a greater number of reasons documented (25 % vs. 9%). Twenty-five percent (23/91) of the sample in the nonadherent group listed all nine reasons for missing medication, while only 9% (10/115) in the adherent group listed all nine. Interestingly, Walsh et al., (2001) documented forgetting as the third highest-ranking reason, with, 'I ate a meal at the wrong time' being the highest followed by 'overslept'. It is however important to note that Walsh et al. (2001) used a list of 21 reasons and conducted the study in a time when ART regimens were very onerous and complex. Walsh's (2001) factor analysis of reasons interestingly found that 'low priority for medication' and 'unintentional non-adherence' were independently associated with non-adherence.

Gaining a clearer understanding of the type of non-adherence can support joint decisions to possibly change patient regimens and/or gain perspective on patient's unique situation. Distinguishing between intentional and unintentional non-adherence may assist in categorizing whether the reasons fall into a certain theme. Understanding the type of theme is a foundation to develop interventions. Wayson Locher, Pargament and Duggan

(2007) conducted seven qualitative interviews with women of color with HIV on the lived experience of ART. Three themes emerged: trust and mistrust (of medicines, clinicians, friends); motivation of approach/avoidance and constantly tethered. They discuss this concept of 'constantly tethered' as derived from having to take pills every day, fear of forgetting, need to create new routines and constant reminder of HIV that having to take the medication created. Nonetheless, not all health care providers are able to interview their patients in order to break through to a theme, but what Wayson Locher, Pargaement and Duggan (2007) draw attention to is that the repeated findings of forgetting or sleeping through a dose may possibly be a manifestation of rebellion or denial against what a life tethered to ART produces. Forgetting, away from home, busy, slept through are easy, quick, uncomplicated answers.

Our study has replicated the findings in other studies that forgetfulness is still the most common reason for non-adherence. Our study discussion also demonstrates the need to begin focusing on patients' unique situation in order to gain an appreciation for the type of non-adherence they are experiencing. More research needs to be conducted to gain insight into the world of intentional and unintentional non-adherence so novel adherence interventions focused in this area can be developed.

The nature of this cross sectional study with self-reported data allows only for a snapshot of what is happening at that specific time. However, adherence is a dynamic issue. Dichotomizing the data for ease of analysis can weaken the results. The ACTGrev was limited to nine reasons. Although, the nine reasons listed are commonly cited in both qualitative and quantitative studies, there was no option for *other*, potentially forcing/pressuring/suggesting to participants to document only the reasons presented.

Nonetheless, the ACTGrev is a quick translatable starting point for a patient-centered approach to assess the need for further adherence counseling. Additionally, using the visual analogue scale with a 3-day recall, rather than 30 day and without another objective measure of adherence restricted our construct validity. The reporting on viral load was self-report and not confirmed with medical records for the entire sample; only a portion of the sample's viral load was taken from chart abstraction. Demographics and clinical characteristics presented a profile of the women for this study, but we did not provide the patient's regimen history, and other patient related factors such as substance abuse, depression, and social support that have been associated with adherence.

Forgetting has dominated the adherence literature, as the leading reason people are not taking their medicines; and even with the influence of reminder devices and strategies, the problem remains. This emphasizes that certain intervention strategies won't work for everyone due to the complex nature of adherence. This evidence also suggests that 'forgetting' is an easy answer to a more complex problem not entirely addressed by a 9-item instrument. As a community of nurses working with PLWHA, we need to meet our patients where they are and realize that their life circumstances change quickly. It is vital that we are not complacent when patients say, "I simply forgot" but be proactive and support patients to discuss what forgetting actually means. Moving toward interpreting the type of non-adherence a person is having, can lead to a more patient-centered approach and influence a new body of literature that may spur new and innovative interventions targeting the type of non-adherence PLWHA are experiencing.

References

Amico, K. R., Konkle-Parker, D. J., Cornman, D. H., Barta, W. D., Ferrer, R., Norton, W. E., et al. (2007). Reasons for ART non-adherence in the Deep South: adherence needs of a sample of HIV-positive patients in Mississippi. *AIDS Care, 19*, 1210-1218.

Arnsten, J. H., Demas, P. A., Grant, R. W., Gourevitch, M. N., Farzadegan, H., Howard, A. A., et al. (2002). Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *Journal of General Internal Medicine, 17*, 377-381.

Atkins, L., & Fallowfield, L. (2006). Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *European Journal of Cancer, 42*, 2271-2276.

Balint, E. (1969). The possibilities of patient-centered medicine. *Journal of the Royal College of General Pracitioners, 17*, 269-276.

Barfod, T. S., Sorensen, H. T., Nielsen, H., Rodkjaer, L., & Obel, N. (2006). 'Simply forgot' is the most frequently stated reason for missed doses of HAART irrespective of degree of adherence. *HIV Medicine, 7*, 285-290.

Catz, S.L., Kelly, J.A., Bogart, L.M., Benotsch, E.G., & McAuliffe, T.L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology*, *19*, 124-133.

Centers for Disease Control and Prevention. *National Women and Girls Awareness Day.* Retrieved September 10, 2011 from http://www.cdc.gov/features/womengirlshivaids/

Daleboudt, G. M., Broadbent, E., McQueen, F., & Kaptein, A. A. (2010). Intentional and unintentional treatment non-adherence in patients with systemic lupus erythematosus. *Arthritis Care Research (Hoboken)*.

Ferguson, T.F., Stewart, K.E., Funkhouser, E., Tolson, J., Westfall, A.O., & Saag, M.S. (2002). Patient-perceived barriers to antiretroviral adherence: Associations with race. *AIDS Care, 14*, 607-617.

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

Heckman, B. D., Catz, S. L., Heckman, T. G., Miller, J. G., & Kalichman, S. C. (2004). Adherence to antiretroviral therapy in rural persons living with HIV disease in the United States. *AIDS Care, 16*, 219-230.

Hill, Z., Kendall, C., & Fernandez, M. (2003). Patterns of adherence to antiretrovirals: why adherence has no simple measure. *AIDS Patient Care STDS, 17*, 519-525.

Holzemer, W. L., Bakken, S., Portillo, C. J., Grimes, R., Welch, J., Wantland, D., et al. (2006). Testing a nurse-tailored HIV medication adherence intervention. *Nursing Research, 55*, 189-197.

Kalichman, S. C., Catz, S., & Ramachandran, B. (1999). Barriers to HIV/AIDS treatment and treatment adherence among African-American adults with disadvantaged education. *Journal National Medical Association, 91*, 439-446.

Kalichman, S. C., Rompa, D., DiFonzo, K., Simpson, D., Austin, J., Luke, W., et al. (2001). HIV treatment adherence in women living with HIV/AIDS: research

based on the Information-Motivation-Behavioral Skills model of health behavior. *Journal of Association of Nurses in AIDS Care, 12*, 58-67.

Kyser, M., Buchacz, K., Bush, T. J., Conley, L. J., Hammer, J., Henry, K., … Brooks, J. T. (2011). Factors associated with non-adherence to antiretroviral therapy in the SUN study. *AIDS Care, 23*, 601-611.

Laws, M. B., Epstein, L., Lee, Y., Rogers, W., Beach, M. C., & Wilson, I. B. (2011).The association of visit length and measures of patient-centered communication in HIV care: A mixed methods study. *Patient Education and Counseling*, (In press).

Lazo, M., Gange, S. J., Wilson, T. E., Anastos, K., Ostrow, D. G., Witt, M. D., & Jacboson, L. P. (2007). Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women. *Clinical Infectious Diseases, 45*, 1377-1385.

Lehane, E., & McCarthy, G. (2007). An examination of the intentional and unintentional aspects of medication non-adherence in patients diagnosed with hypertension. *Journal of Clinical Nursing, 16*, 698-706.

Lopez, E. J., Jones, D. L., Villar-Loubet, O. M., Arheart, K. L., & Weiss, S. M. (2010). Violence, coping, and consistent medication adherence in HIV-positive couples. *AIDS Education and Prevention, 22*, 61-68.

Lowry, K. P., Dudley, T. K., Oddone, E. Z., & Bosworth, H. B. (2005). Intentional and unintentional nonadherence to antihypertensive medication. *Annals of Pharmacotherapy, 39*, 1198-1203.

Mannheimer, S., Friedland, G., Matts, J., Child, C., & Chesney, M. (2002). The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clinical Infectious Diseases, 34*, 1115-1121.

Mannheimer, S. B., Morse, E., Matts, J. P., Andrews, L., Child, C., Schmetter, B., & Friedland, G.H. (2006). Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial. *Journal of Acquired Immune Deficiency Syndrome, 43(*Suppl 1*)*, S41-47.

McNabb, J., Ross, J. W., Abriola, K., Turley, C., Nightingale, C. H., & Nicolau, D. P. (2001). Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic. *Clinical Infectious Diseases, 33*, 700-705.

Mo, P. K., & Mak, W. W. (2009). Intentionality of medication non-adherence among individuals living with HIV/AIDS in Hong Kong. *AIDS Care, 21*, 785-795.

Norton, W. E., Amico, K. R., Fisher, W. A., Shuper, P. A., Ferrer, R. A., Cornman, D. H., ..Fisher, J. D. (2010). Information-motivation-behavioral skills barriers associated with intentional versus unintentional ARV non-adherence behavior among HIV+ patients in clinical care. *AIDS Care, 22*, 979-987.

Okonsky, J. G. (2011). Problems taking pills: understanding HIV medication adherence from a new perspective. *AIDS Care*. Epub.

Ortego, C., Huedo-Medina, T. B., Llorca, J., Sevilla, L., Santos, P., Rodriguez, E., Warren, M.R. & Vejo, J. (2011). Adherence to Highly Active Antiretroviral Therapy (HAART): A Meta-Analysis. *AIDS and Behavior, 15*, 1381-1396.

Phillips, A. N., Neaton, J., & Lundgren, J. D. (2008). The role of HIV in serious diseases other than AIDS. *Aids, 22*, 2409-2418.

Roberts, K. J., & Mann, T. (2003). Adherence to antiretroviral medications in HIV/AIDS care: a narrative exploration of one woman's foray into intentional non-adherence. *Health Care for Women International, 24*, 552-564.

Rochon, D., Ross, M. W., Looney, C., Nepal, V.P., Price, A. J., & Giordano, T. P. (2011). Communication strategies to improve HIV treatment adherence. *Health Communication, 26*, 461-467.

Saha, S., Beach, M.C., & Cooper, L. A. (2008). Patient centeredness, cultural competence and healthcare quality. *Journal of the National Medical Association, 100*, 1275-1285.

Samet, J. H., Libman, H., Steger, K. A., Dhawan, R. K., Chen, J., Shevitz, A. H., …Craven, D.E. (1992). Compliance with zidovudine therapy in patients infected with human immunodeficiency virus, type 1: a cross-sectional study in a municipal hospital clinic. *American Journal of Medicine, 92*, 495-502.

Simoni, J. M., Amico, K. R., Smith, L., & Nelson, K. Antiretroviral adherence interventions: translating research findings to the real world clinic. *Curr HIV/AIDS Rep, 7*(1), 44-51.

Sullivan, P. S., Campsmith, M. L., Nakamura, G. V., Begley, E. B., Schulden, J., & Nakashima, A. K. (2007). Patient and regimen characteristics associated with self-reported nonadherence to antiretroviral therapy. *PLoS One, 2*(6), e552.

Vyavaharkar, M., Moneyham, L., Tavakoli, A., Phillips, K. D., Murdaugh, C., Jackson, K., & Meding G. (2007). Social support, coping, and medication adherence among HIV-positive women with depression living in rural areas of the southeastern United States. *AIDS Patient Care STDS, 21*(9), 667-680.

Wayson Locher, A., Pargament, K., & Duggan, J. (2007). Antiretroviral therapy in the lives of women of colour with HIV. *AIDS Care, 19*, 1048-1051.

Walsh, J. C., Horne, R., Dalton, M., Burgess, A. P., & Gazzard, B. G. (2001). Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care, 13*, 709-720.

Walsh, J. C., Mandalia, S., & Gazzard, B. G. (2002). Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *Aids, 16*, 269-277.

Webel, A.R., Asher, A., Okonsky, J.G., Cuca, Y., Kaihura, A., Dawson-Rose, C. Hanson, J., & Salata, R. (2011). *Measuring HIV Self-Management in Women Living with HIV/AIDS: A Psychometric Evaluation Study of the HIV Self-Management Scale.* Manuscript submitted for publication.

Wilson, I. B. (2010). Improving treatment adherence. *John Hopkins Advanced Studies in Medicine, 10,* 53-57.

Wilson, I.B., for the MACH 14 Investigators. (2010a). A 'honeymoon effect' when initiating the use of electronic drug monitoring (EDM) in clinical studies: findings from MACH14. [Abstract # 62225]. Presented at: 5th International Conference on HIV Treatment Adherence; May 23-25, 2010; Miami, FL. Abstract retrieved from: http://www.iapac.org/AdherenceConference/Downloads-ADC10/Adherence2010_Program_and_Abstracts%20book_051310.pdf

Wilson, I.B., for the MACH 14 Investigators. (2010b). Heterogeneity among studies in rates of declines of antiretroviral therapy (ART) adherence over time: findings from MACH14. [Abstract # 62221]. Presented at: 5th International Conference on HIV Treatment Adherence; May 23-25, 2010; Miami, FL. Abstract retrieved from: http://www.iapac.org/AdherenceConference/Downloads-ADC10/Adherence2010_Program_and_Abstracts%20book_051310.pdf

Wroe, A., & Thomas, M. (2003). Intentional and unintentional nonadherence in patients prescribed HAART treatment regimens. *Psychology Health & Medicine, 8*, 453-463.

Wroe, A. L. (2002). Intentional and unintentional nonadherence: a study of decision making. *Journal of Behavioral Medicine, 25*, 355-372.

Yard, S. S., Huh, D., King, K. M., & Simoni, J. M. (2011). Patient-Level Moderators of the Efficacy of Peer Support and Pager Reminder Interventions to Promote Antiretroviral Adherence. *AIDS and Behavior*. Epub.

Table 1: Demographic and clinical characteristics: Overall and by Adherence level and Regimen

Characteristics	**Overall sample** **n=206** **n (%)**		**Adherent** *100% in past 3 days* **n=115** **n (%)**	**Nonadherent** *Less than 100% in past 3 days* **n=91** **n (%)**		**PI based regimen** **n=99** **n (%)**	**Non-PI based regimen** **n=107** **n (%)**
Age in years: Mean (SD)	47 (9.2)		47 (9.9)	46 (8.3)		47(8.8)	47 (9.7)
Race							
AA	129 (64)		70 (63)	59 (67)		50 (53)	79 (75)
Hispanic	17 (9)		9 (8)	8 (9)		13 (14)	4 (4)
White	38 (19)		24 (21)	14 (16)		22 (23)	16 (15)
Other	16 (8)		9 (8)	7 (8)		10 (10)	6 (6)
Education							
11 grade or less	59 (30)		32 (29)	27 (30)		29 (31)	30 (29)
High School Diploma or General Education Degree	83 (42)		42 (38)	41 (46)		38 (40)	45 (43)
2 years college	42 (21)		26 (23)	16 (18)		22 (23)	20 (19)
4 yrs/MS/PhD	15 (7)		11 (10)	5 (6)		6 (6)	10 (9)
Marital status							
Married	25 (13)		16 (15)	9 (10)		14 (15)	11 (11)
Single	118 (59)		59 (54)	59 (66)		59 (61)	59 (57)
Separated/divorced	38 (19)		23 (21)	15 (17)		16 (17)	22 (21)
Other	18 (9)		12 (10)	6 (7)		7 (7)	11 (11)
Have children[1]	147 (88)		84 (88)	63 (89)		73 (89)	74 (87)
Currently employed	44 (22)		26 (23)	18 (20)		19 (19)	25 (24)
Permanent housing	170 (84)		96 (85)	74 (82)		79 (80)	91 (88)
HIV medication adherence in past 3 days: Mean (SD)	87 (22.71)		100 (0)	71(26.5)		83 (26.5)	91(17.7)
CD4+ T cell count[2]**: cell/mm**[3] **Median (IQR)**	500 (250-772)		515 (266-798)	487 (244-714)		430 (233-700)	585 (297-839)
Detectable HIV Viral Load[3] **(> 75 copies/mL)**	38 (26)		18 (24)	20 (33)		22 (33)	16 (23)
Viral Load: copies/mL **Median (IQR)**	1720 (300-11200)		2865[4] (214-70000)	1720 (412-5100)		3450[4] (302-22260)	640 (227-5015)
Ever told had AIDS	92 (46)		46 (41)	46 (52)		52 (53)	40 (40)

1: 78-81% of sample responded
2: 73-85% of sample responded
3: 66-67% of sample responded
4: Four persons documented a VL ≥100000

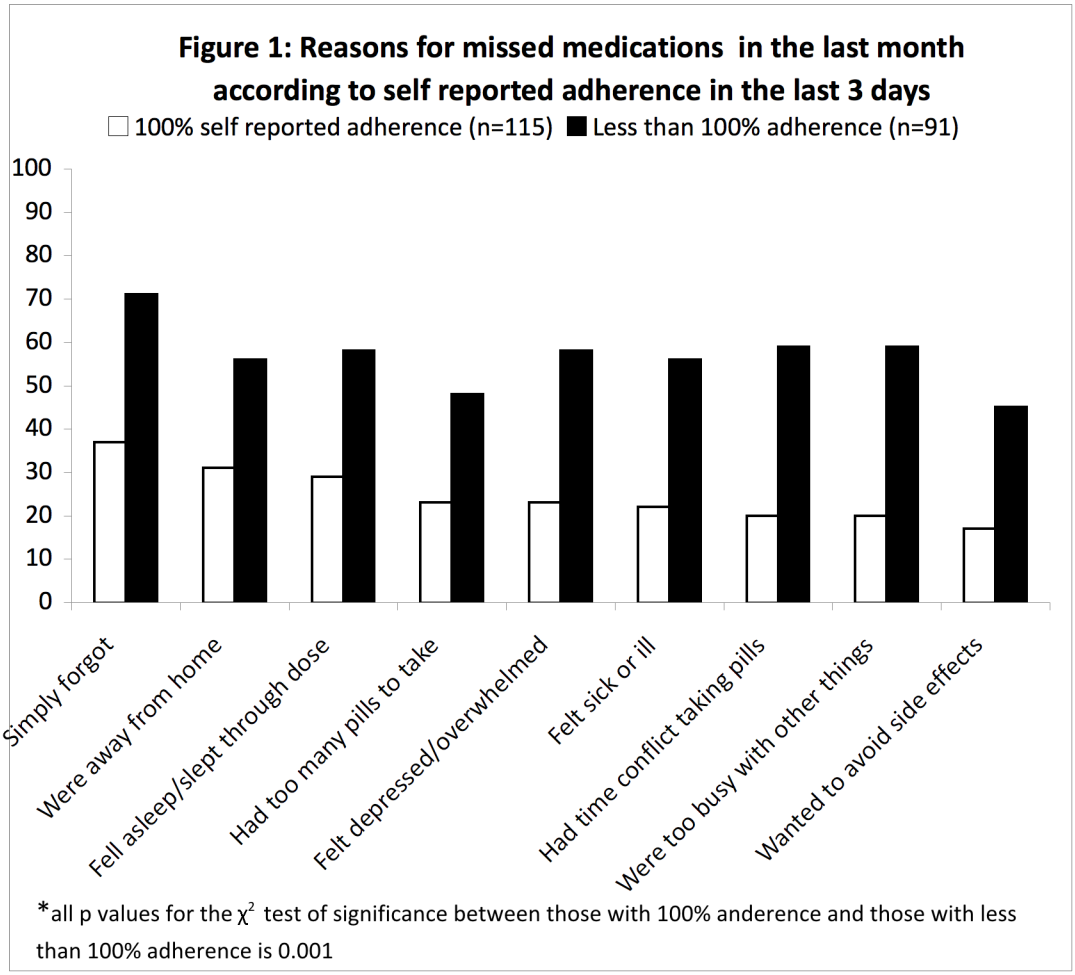


Figure 1: Reasons for missed medications in the last month according to self reported adherence in the last 3 days
100% self reported adherence (n=115)
Less than 100% adherence (n=91)
100
90
80
70
60
50
40
30
20
10
0
Simply forgot
Were away from home
Fell asleep/slept through dose
Had too many pills to take
Felt depressed/overwhelmed
Felt sick or ill
Had time conflict taking pills
Were too busy with other things
Wanted to avoid side effects
*all p values for the χ² test of significance between those with 100% anderence and those with less than 100% adherence is 0.001

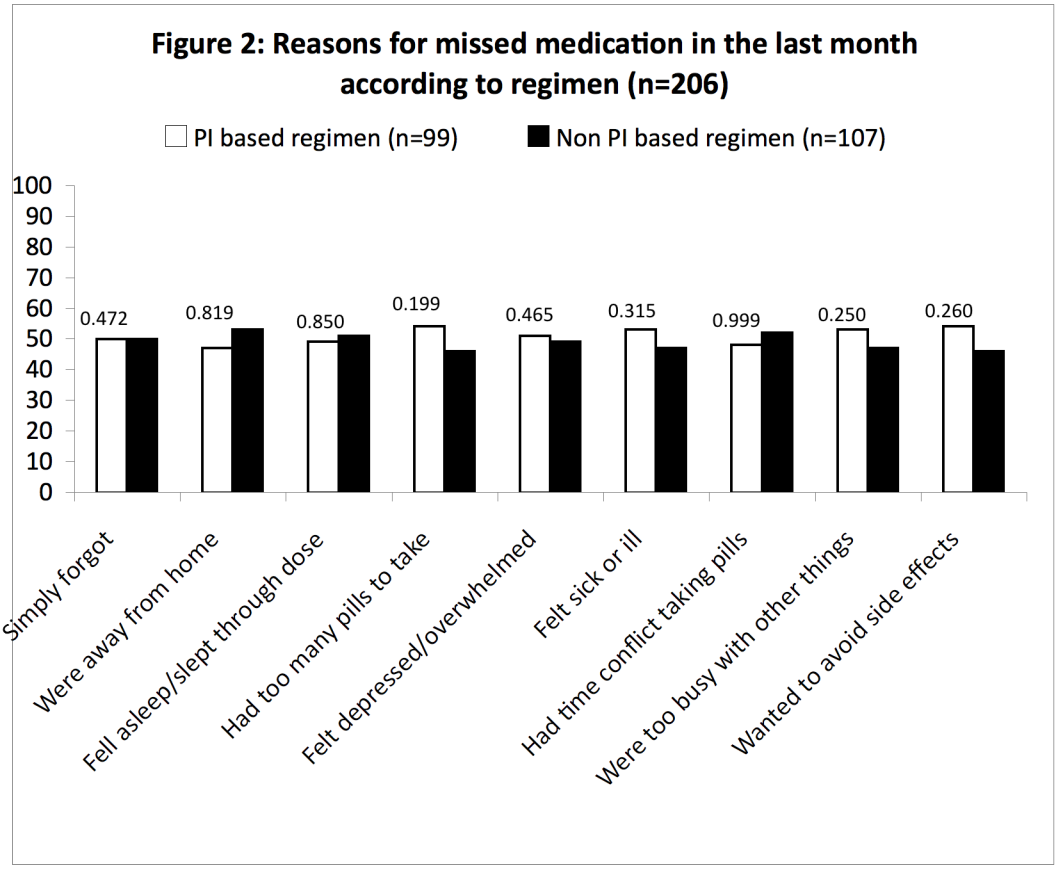
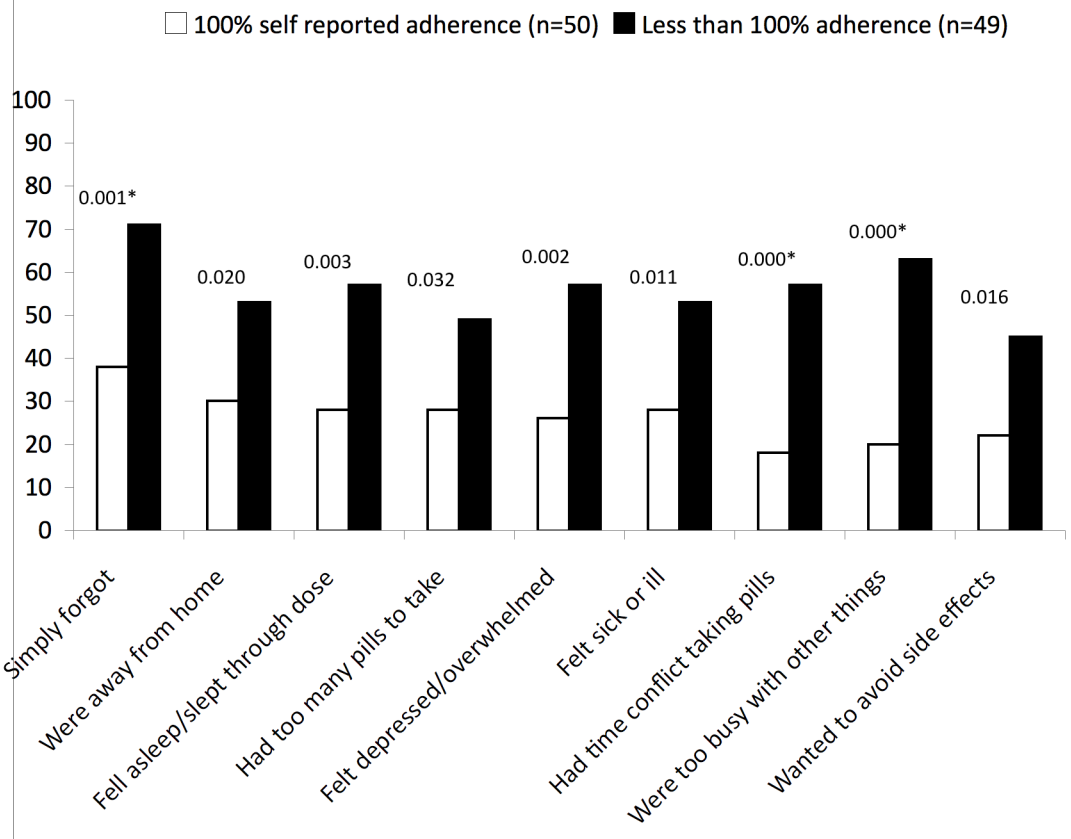


Figure 2: Reasons for missed medication in the last month according to regimen (n=206)
PI based regimen (n=99)
Non PI based regimen (n=107)
100
90
80
70
60
50
40
30
20
10
0
0.472
0.819
0.850
0.199
0.465
0.315
0.999
0.250
0.260
Simply forgot
Were away from home
Fell asleep/slept through dose
Had too many pills to take
Felt depressed/overwhelmed
Felt sick or ill
Had time conflict taking pills
Were too busy with other things
Wanted to avoid side effects

Figure 3: Reasons for missed medications in the last month according to self reported adherence in the last three days for those taking a PI based regimen (n=99)



*χ^2 test of significance between 100% adherent and less than 100% had a p-value <0.001

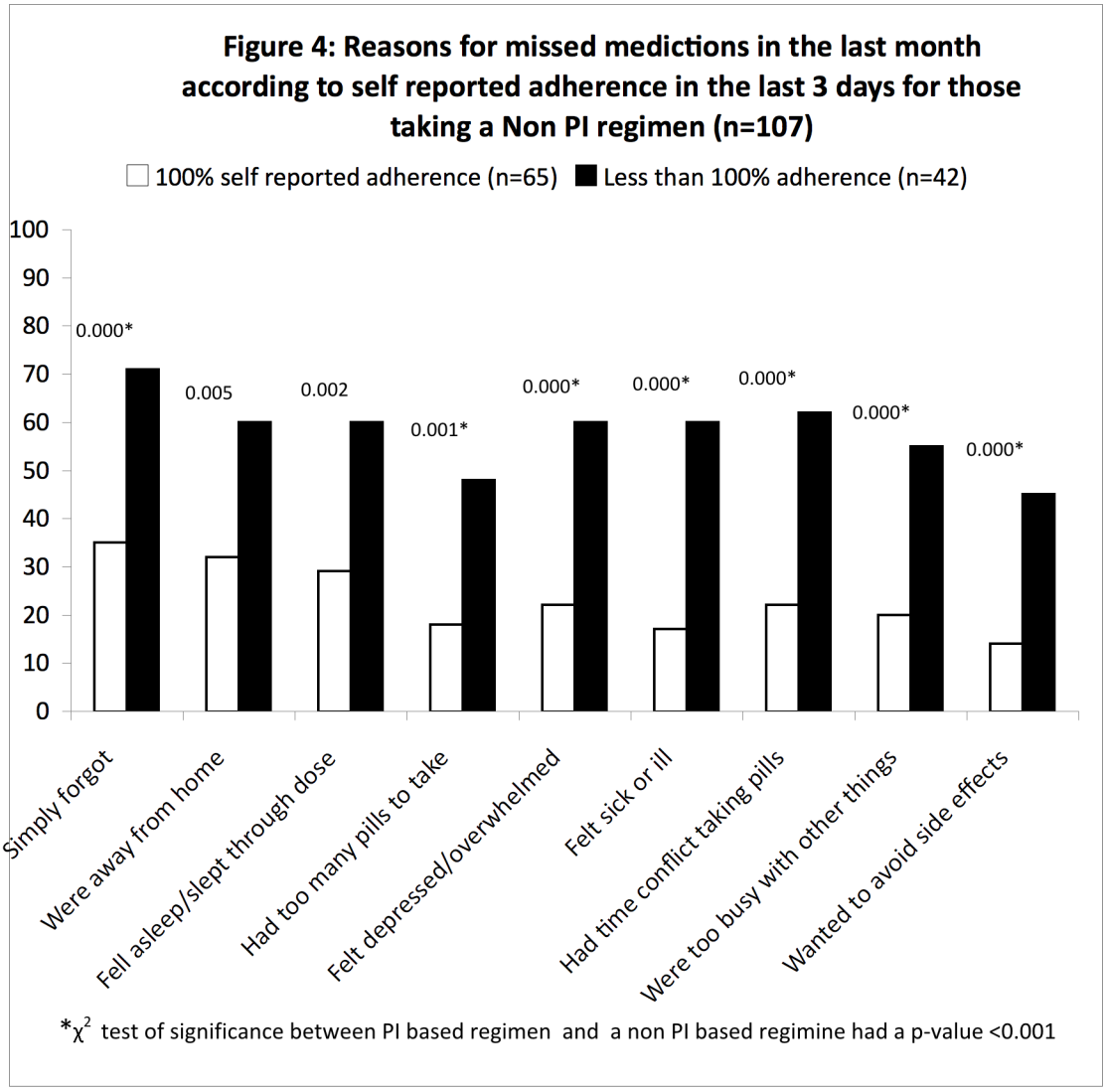


Figure 4: Reasons for missed medictions in the last month according to self reported adherence in the last 3 days for those taking a Non PI regimen (n=107)
100% self reported adherence (n=65)
Less than 100% adherence (n=42)
100
90
80
70
60
50
40
30
20
10
0
0.000*
0.005
0.002
0.001*
0.000*
0.000*
0.000*
0.000*
0.000*
Simply forgot
Were away from home
Fell asleep/slept through dose
Had too many pills to take
Felt depressed/overwhelmed
Felt sick or ill
Had time conflict taking pills
Were too busy with other things
Wanted to avoid side effects
*χ^2 test of significance between PI based regimen and a non PI based regimine had a p-value <0.001

Understanding Reasons for Non-adherence in Women Living with HIV and AIDS Using a Self-Management Framework

Title: Understanding Reasons for Non-adherence in Women Living with HIV and AIDS Using a Self-Management Framework

Abstract

Women living with HIV in the United States taking antiretroviral therapy have reported poorer medication adherence rates compared to men. Gaining an understanding of the relationship between reasons women living with HIV are nonadherent and selected self-management factors is a subsequent step in non-adherence research for women. This cross sectional study in women from two US cities analyzed reasons for non-adherence and found wanting to avoid side effects and being away from home to have a significant difference when associated with race and employment. Findings from this sample highlight the need for ongoing research with women living with HIV.

Introduction

The HIV medication adherence literature is vast and research on women living with HIV has steadily grown. However, studies examining HIV adherence in women, specifically reasons for non-adherence is limited. Women in the United States (US) represent 25% of the newly diagnosed cases of HIV (Centers for Disease Control and Prevention, 2011). Studies on women living with HIV have reported poorer medication adherence compared to men (Arnsten, et al., 2002; Lopez, Jones, Villar-Loubet, Arheart & Weiss, 2010; Puskas et al., 2011; Ubbiali et al., 2008). Although the HIV adherence literature has explored numerous contextual, process and outcome factors, few have examined the reasons for non-adherence in women using a framework that integrates these various factors. Ryan and Sawin's Individual and Family Self-Management Theory organizes the process of self-management into contextual, process, and outcome factors. Framing the many factors associated with non-adherence using Ryan and Sawin's Individual and Family Self-Management theoretical components is particularly relevant to women living with HIV, who are often managing several co-occurring chronic conditions and balancing multiple social and family roles.

Contextual Factors

Despite that the adherence literature is not generally organized into contextual, process and outcome factors, incorporating the many factors into a self-management framework can provide a lens to view the dynamic nature of adherence. According to Ryan and Sawin (Ryan & Sawin, 2009), contextual factors are those related to the individual, family, condition, physical, and social environment, such as access to care,

setting, culture, and social capital. Some research documents that race (Kleeberger et al., 2001; Sullivan et al., 2007), gender (Kuyper et al., 2004; Puskas et al., 2011; Ubbiali et al., 2008), age (Protopopescu et al., 2009), and low income (Kleeberger et al., 2001) are associated with poor adherence, while other studies have contradicted these findings (Ammassari et al., 2002; Atkinson & Petrozzino 2009; Jones et al., 2003). HIV medication regimen complexity and type (dosing, pill burden, adverse effects, protease inhibitors) have also been found to be determinants of non-adherence (Ammassari et al., 2002; Protopopescu et al., 2009; Sullivan et al., 2007) as has literacy (Kalichman, Catz & Ramachandran, 1999; Kalichman & Grebler, 2010). A history of an AIDS diagnosis and being on a protease inhibitor (PI) based regimen are among the factors associated with decreased HIV medication adherence specifically in women (Lazo et al, 2007).

Puskas et al. (2011) published a literature review from 2000 to 2011 on treatment adherence by gender to determine gender differences in non-adherence to ART and found that women are less adherent than men. Sixty-eight percent of the articles reviewed reported women to be less adherent and 18% reported significant differences. The literature suggests that lower adherence may be due to the multiple conditions and various psychological issues women face.

An empirical review of studies that were published between 2006-2008 investigated patient and treatment characteristics associated with non-adherence (Atkinson & Petrozzino, 2009). Predictors of non-adherence were divided into four clusters (clinical, comorbid, treatment competence, and dosing). Treatment competence was defined as the patient's understanding of treatment benefits, treatment self-efficacy, and shared decision-making. The review demonstrated that self-reported symptoms,

stressful life events, lack of social support, regimen complexity, and self-efficacy were consistently associated with adherence to ART; age, race and ethnicity were inconsistently associated with adherence to ART; and gender, education and employment were generally not associated with adherence (Atkinson & Petrozzino, 2009).

In the last decade, social capital has been studied in public health arenas and has been gaining interest among HIV researchers, providers and policy-makers (Lomas, 1998, Islam et al., 2006, Pearce and Davey Smith, 2003; Webel et al., 2011b). Social capital has been defined as the "aggregate or potential resources, which are linked to possession of a durable network of more or less institutionalized relationships of mutual acquaintance or recognition" (Bourdieu, 1985). Existing research on HIV and social capital has primarily focused on HIV transmission prevention (Bhattacharya., 2005; Campbell et al., 2002,; Cené et al., 2011; Holtgrave and Crosby, 2003; Morrison, 2005). Webel et al. (2011b) described the degree of social capital in an international sample of 1,963 adults living with HIV and AIDS from 16 sites in five countries. Their findings included: total mean social capital of 2.68 points with a range of 0-5, (a higher than average total social capital score); and moderate correlations between self-reported physical (r=0.25) and psychological conditions (r=0.36), social support (r=0.31), and total social capital. These findings provide a foundation to build upon how social capital may influence individual-level health.

The overall adherence literature concurs that some contextual factors (treatment complexity, symptoms) are consistently associated with non-adherence and researchers along with health care providers have taken action on developing interventions and strategies to overcome these barriers. Factors such as gender and race have been

typically of interest to researchers, albeit inconsistently associated with adherence (Puskas et al, 2011). Taken together, these contextual variables can be used to describe the individual context which influences the degree to which a woman adheres to her HIV medication and suggest gender-specific adherence support.

Process Factors

Process factors include those pertaining to knowledge and beliefs (self-efficacy), self-regulation skills and abilities (decision making, planning) and social facilitation (influence, support, collaboration). Several studies have examined these factors and their relationship to HIV medication adherence. Jones et al., (2003) in a sample of 174 women from three US cities found that greater participant knowledge regarding HIV, HIV medications, and the immune system was related to higher HIV medication adherence. Coping by denial, substance use, and behavioral disengagement were associated with lower HIV medication adherence. Vyavaharkar et al., (2007) examined socio-demographic and social support as antecedent variables and coping as mediating variables on HIV medication adherence. Medication adherence was measured by self-reported missed HIV medications and reasons for missed medications in the last month. The study included 224 women taking antiretroviral therapy (ART) from three rural areas of the Southeastern US. Eighty-two percent were African American, 41% with less than a high school degree, and 79% unemployed. Fifty-nine percent were considered nonadherent (missed at least one dose in the past month). Coping by denial/avoidance and number of children were positively correlated with reasons for missed medications (non-adherence), while coping by managing HIV disease was a negative predictor for

reasons of missed medications (i.e. those who had better self-management skills missed fewer medication doses).

Studies have also examined the cognitive and behavioral correlates of adherence and the role of theory and mediation. Simoni, Frick & Huang, (2006) tested a cognitive-affective model of medication adherence based on social support theory in 136 men and women living with HIV. They found that social support was associated with less negative affect, and greater spirituality, which were associated with self-efficacy to adhere. Johnson et al., (2006) explored a model of medication adherence in which HIV medication adherence self-efficacy mediates the association between positive provider interactions and self-reported adherence. This study used a sample of 2,765 adults living with HIV from four US cities; 74% male, 49% African American, and 54% receiving care from a HIV specialty clinic. Johnson and colleagues found evidence that positive provider interactions were associated with greater adherence self-efficacy, which was associated with better HIV medication adherence.

Outcome Factors

Outcome factors include both proximal (self-management behaviors) and distal outcomes (health status, quality of life and cost of health). Marelich and Murphy, (2003) suggested that HIV infected women who exhibited empowered behaviors reported greater decision-making involvement and had higher levels of communication with their providers. Bakken et al., (2000) examined 707 persons, 77% male, 39% African American, 41% with current or past history of intravenous drug use and a mean of 7.4 (SD=4.1) years known HIV infected. They found those who reported more engagement

with their providers had greater adherence (p=.005). The mean engagement score was 18.6 (SD=7.9; range 13-52, with lower scores indicating more engagement). Our study categorized engagement with health care provider as an outcome; appreciating that as engagement with health care provider increases it also increases the individual's quality of life and health status.

Analyzing the reasons for non-adherence and understanding the relationship with other factors has been studied but is limited (Amico et al., 2007; Barfod et al., 2006; Kalichman, Catz & Ramachandran, 1999; Ferguson et al., 2002; Vyavaharkar et al., 2007; Walsh, Horne, Dalton, Burgess & Gazzard, 2001). Amico et al. (2007) conducted a study to identify common reasons for non-adherence to ART, in those who reported missing a dose of medication in the past three days, and the impact of gender, economic disparities, employment status and depression on reported barriers to adherence. Seventy-two men and women, (44% female), 71% unemployed, and 67% with an education level of high school or less made up the sample. A list of 14 reasons for non-adherence was used. Total number of reasons endorsed was not correlated with rates of adherence. Those who reported a greater number of reasons were women, those unemployed, moderately to severely depressed, and had education level of high school or below. The top five reasons for missing a dose were (1) not having the medication with them, (2) sleeping through the dose time, (3) running out of the medication, (4) being busy with other things, and, (5) other. Wanted to avoid side effects consistently ranked in the lower five reasons and simply forgot was not on the reasons list. Amico et al. (2007) found significant differences mostly between men and women. Women reported, not having the

medication with them, feeling sick, not wanting people to see them take the medicine and wanting a break more frequently than men.

Ferguson et al., (2002) found that in a sample of 149 persons, women were more likely than men to report non-adherence due to forgetting to refill medications and not understanding how to take them. Barfod et al. (2006) examined 840 Danish HIV infected men and women and found no difference in reasons between adherent and nonadherent participants.

Gaining an understanding of the relationship between reasons women living with HIV are nonadherent and selected self-management factors (contextual, process and outcome) is a subsequent step in non-adherence research for women. This framework can support interventions to improve self-management in women living with HIV who are challenged with adhering to their HIV medications. The purpose of this study was to explore reasons for non-adherence, and their associations with selected contextual, process and outcome variables. Focusing specifically on nonadherent women can provide a lens to understand the magnitude of the factors and not the adherence level. This study assessed HIV-infected women, primarily African American, from two cities in the US who reported missing a dose of medication in the past three days. Demographic and clinical characteristics, access to care and social capital were grouped into contextual factors. Chronic disease self-efficacy a process factor, and the outcome factors were level of engagement with health care provider, level of adherence, and reasons for non-adherence.

Methods

Procedures

A cross-sectional study focused on women living with HIV/AIDS was conducted in Cleveland, Ohio and the San Francisco Bay Area of California from October 2010 through March 2011. Inclusion criteria consisted of women 18 years and older, female, confirmed HIV serostatus, English speaking and able to provide informed consent. Participants were recruited from medical clinics and community support organizations. The Institutional Review Boards at both University Hospitals, Case Medical Center and University of California San Francisco (UCSF) approved the study protocol. The study data were collected using a self-administered questionnaire taking 45-60 minutes to complete. This paper focused on nonadherent women who were taking antiretroviral therapy (ART). Non- adherence was defined as less than 100% adherence in the past three days using a self-reported visual analog scale. The primary study protocol was to develop and validate a *HIV Self-Management Scale* for women, (Webel et al., 2011a).

Measures

The self-administered questionnaire packet included information that can be grouped into contextual, process and outcome factors. The scales were chosen based on Ryan and Sawin's Individual and Family Self-Management Theory (Ryan and Sawin, 2009). For the purposes of this study only selected demographic and clinical items and the following scales were included in the analysis: AIDS Clinical Trials Group Revised (ACTGrev) Reasons for Missed Medications, 3-day VAS, Access to Care, Social Capital, Chronic Disease Self-efficacy, and Engagement with Health Care Provider.

Contextual factors

The contextual factors included: demographic (age, race, education level, martial status, children, employment, housing) and clinical items (CD4+ T-cell count, viral load, AIDS diagnosis, regimen), access to care, and social capital. The medication data was dichotomized into those taking a protease inhibitor (PI) based regimen and those taking a non-PI based regimen (from a list of 32 FDA approved HIV medications). Access to care and transportation were assessed using Cunningham's *Access to Care Instrument*, a valid survey among people living with HIV (Cunningham, 1995). For our study, we modified the instrument by adding three items to assess accessibility of transportation. These items were scored as single item indicators (Cunningham 1999). A score of 36-45 indicated poor access to care. The perceived social environment was assessed using the *Social Capital Scale* (Onyx & Bullen, 2000). This 31-item scale was developed in a sample of 1,211 Australian adults. We modified the scale to exclude five work-related items, due to anticipated low employment in our sample. We have used this method in previous studies and have found acceptable psychometric properties in adults living with HIV/AIDS (Webel et al., 2011a). The mean score was calculated and ranged from 1 to 4. High social capital was defined as a mean score of 2.51 or higher (Diaz, Drumm, Ramirez-Johnson, & Oidjarv, 2002).

Process factors

Self-efficacy was assessed using the abbreviated *Chronic Disease Self-Efficacy (CDSE) Scale* (Lorig et al., 1996). This is a 6-item scale assessing self-efficacy related to managing a chronic disease, derived from a larger 33-item scale. The abbreviated version measured four different dimensions including, symptom control, role function, emotional

functioning and communicating with physicians. The mean score was calculated and has a range of 1-10. High CDSE is considered to be a mean score greater than 6.

Outcome factors

Outcome factors included Engagement with Health Care Provider, self-reported HIV medication adherence, and ACTGrev, reasons for missed medications. We assessed engagement with health care provider by administering the *Engagement with Health Care Provider Scale*, a validated 13-item scale in which participants rate the nature of their interactions with their health care providers. Engagement with heath care provider included five dimensions: access to health care provider, information sharing, involvement in decision making and self care activities, respect and support of the provider for client's choices and management of client concerns. The mean score was calculated on a range from 1-4 and engagement was considered high if the mean was equal to or less than 1, lower scores indicate the client is more engaged (Bakken et al., 2000).

Self-reported HIV medication adherence was collected using a 3-day recall visual analogue scale. The scale is based on Walsh, Mandalia and Gazzard, (2002) 30-day assessment. Participants marked their level of adherence (0-100%) for the past three days. Non-adherence was defined as anything less than 100% (Johnson, Dilworth, Taylor, & Nielands, 2011; Lazo et al., 2007). It is common for people to over-report their adherence and thus we choose a conservative definition.

Reasons for Non-adherence

The ACTGrev Reasons for Missed Medications (Holzemer et al., 2006) is a nine-item, self-report measure capturing reasons for missed medications in the last month. The reasons for missed medications factor into two subscales: (1) problems taking pills and (2) forgetfulness. A four-point Likert scale allows participants to respond on the frequency of missing their medications with never, rarely, sometimes or often. The problems taking pills factor includes five items: (1) wanted to avoid side effects, (2) felt sick or ill, (3) too many pills to take, (4) felt depressed/overwhelmed and (5) problems taking pills at specified times. The other four items factor into forgetfulness: (1) too busy with other things, (2) away from home, (3) simply forgot, and (4) fell asleep/slept through the dose.

Analysis

Data analysis was conducted using Stata 10.0 (Statacorp, College Station, TX). The analysis focused on nonadherent participants. This study was motivated by a study conducted by Amico et al., (2007) which identified reasons for non-adherence and the impact of gender, employment, education and depression on reported barriers to adherence. Our study examined additional factors that have been found to be determinants of non-adherence. The nonadherent participants were categorized into eight groups: Race (African Americans vs. other), Education (High school or lower vs. Beyond high school), Employment (Work for pay vs. Not working for pay), Regimen (PI based vs. non-PI based), AIDS diagnosis (Yes vs. No), Engagement with Health care Provider (High vs. Low), Chronic Disease Self-Efficacy (High vs. Low), Social capital (High vs.

Low). Descriptive statistics were calculated for demographic and clinical characteristics. The association of group on documented reasons for non-adherence was evaluated with chi-square tests. Independent t-tests evaluated the adherence levels between group membership. The ACTGrev instrument was calculated and analyzed with those who *ever* missed a medication for the reason. An overall frequency was described regarding the number of reasons given per person. The Access to Care, Social Capital, CDSE, and Engagement with Health Care Provider scales were dichotomized into high and low. Access to care cutoff for high was > 36, Engagement with Health care provider cutoff indicating (high) more engagement was ≤ 1, CDSE cutoff indicating high self-efficacy was > 6 and the cutoff for high social capital > 2.5 (the cutoffs for access to care and social capital have been previously documented in the literature). A multi level predictor analysis was not examined due to the low significant findings.

Results

Participants

The overall sample consisted of 266 women from Cleveland, Ohio and the San Francisco Bay Area, California. Of the 206 that were actively taking antiretroviral medication, 46% (n=91) were categorized as nonadherent and were included in the analysis. Sixty-five percent of the nonadherent sample was African American (n=59), 46% (n=41) had a High school diploma or GED, 30% (n= 27) had less than a 12^{th} grade education, 66% (n=59) single, 89% (n=63) have children and 20% (n=18) were working for pay. The mean self-reported adherence level was 71% (SD: 26.5), mean CD4+ T cell count of 514 (SD: 338.1 and range of 37-1600), 33% (n=20) had detectable viral loads,

and of those the median viral load was 1720 (IQR: 412-5100), 52% (n=46) had ever been told they had AIDS and 54% (n=49) were taking a PI based regimen. Refer to Table 1. Social Capital and CDSE were found to have the majority of the sample categorized into the high cutoff, (65%, 68% respectively, see table 3). Forty-three percent were more engaged with their health care provider. No one in the sample was considered to have poor access to care and transportation. Among the groups that had a lower mean adherence were: African Americans, those educated beyond high school, were working for pay, were taking a PI based regimen, and were never were told they had AIDS. Those that had scored low on Social Capital and CDSE, had a lower mean adherence and those with more engaged with their health care provider also reported a lower mean medication adherence level. Refer to Table 2 for the overall scale score summaries. Independent t-tests showed a significant difference among the PI based versus non-PI based regimen group in mean adherence (p=.03). Refer to Table 3.

Reasons for missed HIV medication

The mean number of reasons for missed medications endorsed by the participants was 5.12 out of 9 (SD: 3.36). At the 25th percentile 2 reasons were provided, 50th percentile increases to 6 and the 75th percentile has all nine reasons. Overall, the most frequent reason documented was simply forgot (71%) and the least common was wanted to avoid side effects (45%). Refer to Figure 1.

Race, Employment

In regard to group membership, wanting to avoid side effects and being away from home were the only two reasons with a significant difference between groups. African Americans had a significantly higher percentage (p=.05) of documenting wanting

to avoid side effects than did women of other races (White/non Hispanic, Asian, Hispanic, Native American). Sixty-one percent of the women who did not work reported being away from home compared to 33% of those who did work (p= .03). There were no other significant differences found between reasons and group membership.

Education

Women who had attained education beyond high school had higher frequencies under the forgetfulness factor reasons (were too busy with other things, away from home, simply forgot, fell asleep/slept through dose) and a lower mean adherence (71.4% vs. 70.2%). The women who had a high school education or lower had higher frequencies in reporting the reasons: felt sick and had too many pills to take.

Medication Regimen, AIDS

Those on a PI based regimen versus a non-PI based regimen were fairly balanced in responses, but those on PI regimen had lower mean adherence (65.7% vs. 77.3%). Those who reported ever having been told they had AIDS had consistently higher frequencies in all nine reasons, but a higher mean adherence (72.6% vs. 69%).

CDSE, Social Capital, Engagement with Health Care Provider

Higher frequencies for most reasons and lower mean adherence levels were reported in the participants categorized into having low chronic disease self-efficacy (CDSE) and low social capital, with a larger difference in the problems taking pills factor (see figures 2 and 3). The women in the sample that fell into the low engagement with health care provider categories had comparable but higher frequencies for all reasons, except for simply forgot (see figure 2). They also had a higher a mean adherence level (75.7% vs. 64.8%). Additionally, wanted to avoid side effects and had too many pills to

take, were noticeably lower in the high engagement with health care provider group (see figure 3).

Discussion

Overall in this sample of nonadherent, mostly African American (67%), single (66%), unemployed (80%) women taking ART, only two reasons for non-adherence were associated with any factor. The two of eight factors examined in association with reasons for non-adherence that were found to be significant, were contextual factors (race and employment). African Americans and those working for pay were associated with wanting to avoid side effects and being away from home, respectively. The mean number of reasons documented by the participants was 5.12 (SD: 3.36) out of a total of nine. The most frequent reason documented was simply forgot (71%) and the least common was wanted to avoid side effects (45%). Frequency of reasons did not always match with adherence level, (i.e. a higher frequency of reasons mean less adherence) highlighting that reasons for non-adherence should be viewed as discrete. Women taking a PI based regimen had a significantly lower mean adherence level than those on a non-PI based regimen (66 vs. 77; p=.03) and those scoring as high engagers with their health care provider had a lower, although not significant, mean adherence level (65 vs. 76; p=.06). The remaining contextual, process and outcome factors do provide valuable information that demonstrates the complex nature of medication adherence in HIV infected women. Appreciating the dynamic nature of adherence and self-management behavior allows for an avenue to translate the findings. Viewing these results within a self-management

framework is helpful in understanding how the reasons for non-adherence relate to the factors integrated into chronic disease self-management.

Education

Our sample of women who had beyond a high school education (25%) consistently reported higher frequency with all nine reasons had a slightly lower mean adherence level (71.4 vs. 70.2). Simply forgot had the highest frequency with 78%. Felt sick and had too many pills to take were the only two reasons of the nine that were not reported more frequently in the beyond high school group. Our finding contradicts other studies (Amico et al., 2007; Kalichman, Catz & Ramachandran, 1999; Murphy, Greenwell, & Hoffman, 2002). Kalichman, Catz and Ramachandran (1999) found that men and women with lower education literacy reported higher frequencies in 11/14 reasons. The reasons: forgot, something unexpected came up and traveling were the three reasons the higher education literacy group reported more of. Murphy, Greenwell, & Hoffman (2002) conducted a study with 45 HIV infected women with children. Fifty-nine percent were African American; mean CD4+ T cell count 486 cells/mm^s and a mean 3-day adherence rate of 56%. They found that women with higher education were more likely to be adherent than women with lower education (OR: 1.53). Amico et al., (2007) found those with a high school education and lower reported higher frequencies except for the reasons was busy with other things and was not feeling sick. Kalichman and Amico studies found that those with less education reported higher frequency of reasons, while our study found the opposite. Of note is that although education in years and education literacy can not be equally compared and the samples in these studies were not identical, the comparison and contradictory evidence may highlight that the influence of

education on adherence may be more individual and in fact may vary in women who may be juggling multiple self-management tasks. Additionally, it highlights that reasons and adherence is not a cumulative phenomenon but rather each reason is discrete and not necessarily correlated with rates of adherence (Amico et al., 2007).

Employment

Our study also found those unemployed consistently reported more reasons. Being away from home was the one reason that showed a significant difference (p=.03) in our study. Sixty-one percent of women who were unemployed (not working for pay) compared to 33% of women who were employed reported the reason away from home as the barrier to adherence. Amico et al., (2007) also found those who were unemployed consistently reported more reasons, (exception being slept through the dose). The reason, did not want people to see me taking HIV medication, had a significant difference between the unemployed and employed (endorsed more so for the unemployed). It is unclear how many women fall under the employed group in the Amico et al., (2007) study and what their overall adherence was, nonetheless an interesting finding to see the influence of employment on reasons for non-adherence. Our sample of women, who were employed, had a lower mean adherence (66% vs. 73%). It is possible that as women with HIV live longer they will re-enter the work force and this may consequently have a negative influence on their adherence. Therefore, it is necessary to support women in choosing jobs that will allow for privacy and self-management of their disease (Webel & Higgins, 2011).

Regimen, AIDS diagnosis

Our study did not find an association between reasons and type of regimen (PI vs. non-PI), but did find a significant difference between mean adherence level between the regimen groups. Atkinson and Petrozzino, (2009) in their empirical review comparing patient and treatment characteristics on non-adherence behavior and treatment failure found that PI based regimens had a consistent negative effect on adherence behavior. AIDS diagnosis, although contradictory in the literature regarding its impact on adherence, demonstrated that women in this sample who were ever told they had AIDS, had consistently higher frequencies for each reason, but also a higher self-reported mean adherence (73% vs. 69%). These findings can be viewed as contradictory, possibly suggesting that perhaps those who were ever told they had AIDS have had different experiences with their degree of illness, motivating them to stay on target with their adherence, yet still having more a variety of reasons for their non-adherence. Additionally, it is possible that they are reporting more reasons due to their openness and acceptance since being classified as having AIDS.

CDSE, Social Capital

Not surprising, trends were noted in those grouped into low CDSE and low social capital as having higher frequencies for each reason and worse adherence. Reviewing the concept of self-efficacy and the research in this area, our finding is consistent with the existing literature. Social capital and its intersection with adherence allows for this finding to be built upon in order to gather a body of research that uses social capital in women and understand how it can be integrated into ART adherence interventions.

Engagement

The women who reported low engagement with their health care provider were fairly consistent with documenting higher frequencies for most reasons, but interestingly had a higher mean adherence (75% vs. 65%; p= .06). The women who reported having better engagement, reported simply forgot most frequently. This may highlight that reporting simply forget is an easy answer (Okonsky et al., 2011*)*, and for some women, with a high level of engagement with their providers, may not want to let their providers down and forgetting is a common and acceptable reason. Also of interest, is that high engagers had a lower reported frequency with the reasons, wanted to avoid side effects and had too many pills to take, (which are two documented barriers). Qualitative research with women has demonstrated the themes of trust, coping, avoidance, and lack of empowerment as barriers to adherence (Jones et al., 2003; Wayson Locher, Pargament, & Duggan, 2007), while integrating engagement and communication strategies for improving adherence has been positive. Although these findings on engagement may seem contradictory, in that the low engagers in this sample had better adherence, these results are to be viewed with caution. The study was cross sectional and Engagement with Health Care Provider scale was dichotomized. In spite of this, what the findings suggest in regard to adherence and self-management is that the intersection of engagement as an outcome is related to behavior and adherence within the multiple roles women living with HIV are managing.

Limitations

The access to care scale mean score was 21.86, indicating that no one in this sample was considered to have poor access. Although this finding does present a positive view, the sample of women were all attending HIV specialty clinics in urban areas, resulting in potentially skewed results that may not be applicable to rural areas. However, the demographic make up of the sample is similar to those women in rural areas. This study was also limited since no information on substance abuse or depression was collected, (two documented determinants of non-adherence). Self-reporting of clinical items and the assessment of the reasons for non-adherence did not allow for open ended questions or dialogue regarding other roles or complexities that the women were currently facing. And although the reasons for missed medications (ACTGrev) scale is limited, the nine reasons for non-adherence are often used in other adherence research. Additionally, using the visual analogue scale with a 3-day recall, rather than a 30 day and without another objective measure of adherence restricted our construct validity. The reporting on viral load was self-report and not confirmed with medical records for the entire sample; only a portion of the sample's viral load was taken from chart abstraction. Dichotomizing the sample weakened the power of the study, but does provide a starting point for further investigation of various contextual, process and outcome factors associated with non-adherence.

Conclusion

In general, women taking ART who have self-reported non-adherence provide a complex profile. The findings from this sample of women continue to highlight the need for ongoing research with women living with HIV. The research on reasons for non-

adherence in women needs to be continually addressed from both quantitative and qualitative approaches. Understanding the reasons for non-adherence in women as discrete reasons associated with various contextual, process and outcome factors in a self-management framework provides foundational information to build upon. Framing HIV adherence research and intervention development using self-management components can help facilitate the integration of theory and empirical data that may result in women living with HIV and AIDS managing, balancing and improving their overall individual and family health.

References

Ammassari, A., Trotta, M.P., Murri, R., Castelli, F. Narciso, P., Noto, P., … AdiCoNA Study Group. (2002). Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *Journal of Acquired and Immune Deficiency Syndromes, 15,* S123-127.

Amico, K. R., Konkle-Parker, D. J., Cornman, D. H., Barta, W. D., Ferrer, R., Norton, W. E., et al. (2007). Reasons for ART non-adherence in the Deep South: adherence needs of a sample of HIV-positive patients in Mississippi. *AIDS Care, 19*, 1210-1218.

Arnsten, J. H., Demas, P. A., Grant, R. W., Gourevitch, M. N., Farzadegan, H., Howard, A. A., & Schoenbaum, E. E. (2002). Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *Journal of General Internal Medicine, 17*, 377-381.

Atkinson, M.J. & Petrozzino, J.J. (2009). An evidence-based review of treatment-related determinants of patients' Nonadherence to HIV medications. *AIDS Patient Care and STDs, 23,* 90-914.

Bakken S., Holzemer W. L., Brown M. A., Powell-Cope, G. M., Turner, J.G., Inouye, J., Nokes, K. M., & Corless. I. B. (2000). Relationships Between Perception of Engagement with Health Care Provider and Demographic Characteristics, Health Status, and Adherence to Therapeutic Regimen in Persons with HIV/AIDS. *AIDS Patient Care and STDs, 14,* 189-197.

Bhattacharya, G. 2005. Social capital and AIDS risk among acculturating Asian Indian men in New York. *AIDS Education & Prevention, 17***,** 555-567.

Bourdieu P. (1985). The forms of capital. *In:* RICHARDSON, J. (ed.) *Handbook of Theory and Research for the Sociology of Education.* New York: Greenwood.

Campbell, C., Williams, B. & Gilgen, D. (2002). Is social capital a useful contextual tool for exploring community level influences on HIV infection? An exploratory case study from South Africa. *AIDS Care, 14***,** 41-54

Cene´, C., Akers, A., Lloyd, S., Albritton, T., Powell Hammond, W. & Corbie-Smith, G. (2011). Understanding Social Capital and HIV Risk in Rural African American Communities. *Journal of General Internal Medicine, 26*, 737-744

Centers for Disease Control and Prevention. *National Women and Girls Awareness Day.* Retrieved September 10, 2011 from http://www.cdc.gov/features/womengirlshivaids/

Cunningham W.E., Ron D. H., Williams K.W., Beck K.C., Dixon W.J., & Shapiro M.F. (1995). Access to Medical Care and Health-Related Quality of Life for Low-Income Persons with Symptomatic Human Immunodeficiency Virus. *Medical Care, 33*, 739-754.

Cunningham W.E., Andersen R.M., Katz M.H., Stein, M.D., Turner, B. J., Crystal, S. … & Shapiro, M. F. (1999). The impact of competing subsistence needs and barriers on access to medical care for persons with human immunodeficiency virus receiving care in the United States. *Medical Care, 37,*1270-1281.

Diaz, H.L., Drumm, R.D, Ramirez-Johnson, J., & Oidjarv, H. (2002). Social capital, economic development and food security in Peru's mountain region. *International social work. 45,* 481-495.

Ferguson, T.F., Stewart, K.E., Funkhouser, E., Tolson, J., Westfall, A.O., & Saag, M.S. (2002). Patient-perceived barriers to antiretroviral adherence: Associations with race. *AIDS Care, 14*, 607-617.

Holtgrave, D. R. & Crosby, R. A. (2003). Social capital, poverty, and income inequality as predictors of gonorrhoea, syphilis, chlamydia and AIDS case rates in the United States. *Sexually Transmitted Infections, 79***,** 62-64.

Holzemer, W. L., Bakken, S., Portillo, C. J., Grimes, R., Welch, J., Wantland, D., & Mullan J. T. (2006). Testing a nurse-tailored HIV medication adherence intervention. *Nursing Research, 55*, 189-197.

Islam M. K., Merlo, J., Kawachi, I., Lindstrom, M. & Gerdtham, U. G. (2006). Social capital and health: Does egalitarianism matter? A literature review. *International Journal for Equity in Health,* 5**,** 3.

Johnson, M. O., Chesney, M. A., Goldstein, R. B., Remien, R. H., Catz, S., Gore-Felton, C., … & NIMH Healthy Living Project Team. (2006). Positive provider interactions, adherence self-efficacy, and adherence to antiretroviral medications among HIV-infected adutlts: A mediation model. *AIDS Patient Care and STDs, 20,* 258-268.

Johnson, M. O., Dilworth, S. E., Taylor, J. M., & Neilands, T.B. (2011). Improving coping skills for self-management of treatment side effects can reduce antiretroviral medication nonadherence among people living with HIV. *Annals of Behavioral Medicine, 41,* 83-91.

Jones, D.L., Ishii, M., LaPerriere A., Stanley H., Antoni, M., Ironson, G., … & Weiss, S. M. (2003). *AIDS Care, 15,* 463-474.

Kalichman, S. C., Catz, S., & Ramachandran, B. (1999). Barriers to HIV/AIDS treatment and treatment adherence among African-American adults with disadvantaged education. *Journal National Medical Association, 91*, 439-446.

Kalichman S. C. & Grebler, T. (2010). Stress and poverty predictors of treatment adherence among people with low-literacy living with HIV/AIDS. *Psychosomatic Medicine, 72,* 810-816.

Kleeberger, C. A., Phair, J. P., Srtrathdee, S. A., Detels, R., Kingsley, L., & Jacobson L. P. (2001). Determinants of heterogeneous adherence to HIV-antiretroviral therapies in the mulitcenter AIDS cohort study. *Jounral of AIDS, 26,* 82-92.

Kuyper, L. M., Wood, E., Montaner J. S. Yip, B., OConnell, J. M., & Hogg, R. S. (2004). Gender differences in HIV-1 RNA rebound attributed to incomplete antiretroviral adherence among HIV-infected patients in a population-based cohort. *Journal of Acquired Immune Deficiency Syndromes, 37,* 1470–1476

Lazo, M., Gange, S. J., Wilson, T. E., Anastos, K., Ostrow, D. G., Witt, M. D., & Jacboson, L. P. (2007). Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women. *Clinical Infectious Diseases, 45*, 1377-1385.

Lomas, J. (1998). Social capital and health: Implications for public health and epidemiology. *Social Science & Medicine, 47,* 1181-1188.

Lopez, E. J., Jones, D. L., Villar-Loubet, O. M., Arheart, K. L., & Weiss, S. M. (2010). Violence, coping, and consistent medication adherence in HIV-positive couples. *AIDS Education and Prevention, 22*, 61-68.

Lorig K., Stewart A., Ritter P., González V., Laurent D., Lynch J. (1996). Outcome Measures for Health Education and other Health Care Interventions. Thousand Oaks CA: Sage Publications, pp. 24-25, 41-45.

Marelich, W. D. & Murphy, D. A. (2003). Effects of empowerment among HIV-positive women on the patient-provider relationship. *AIDS Care, 15,* 475-481.

Morrison, S. D. 2005. Social capital, health and HIV awareness of girls in a rural Caribbean community. *The International Electronic Journal of Health Education, 8***,** 135.

Murphy, D. A., Greenwell S., Hoffman,D. (2002). Factors Associated with Antiretroviral Adherence Among HIV-Infected Women with Children, *Women & Health, 36,* 97-111.

Okonsky, J. G., Webel, A., Dawson-Rose, C., Johnson, M., Asher, A., Cuca, Y., … Portillo, C. J. (2011). Not *Just* Simply Forgetting: Appreciating Reasons for Non-adherence in Women by Adherence Level and Regimen. Manuscript submitted for publication.

Onyx J., & Bullen P. Measuring Social Capital in Five Communities. (2000). *Journal of Applied Behavioral Science,* 36, 23-42.

Pearce, N. & Davey Smith, G. (2003). Is Social Capital the Key to Inequalities in Health? *American Journal of Public Health, 93***,** 122-129.

Portes, A. (1998). Social Capital: Its Origins and Applications in Modern Sociology. *Annual Review of Sociology, 24***,** 1-24.

Pronyk, P. M., Harpham, T., Morison, L. A., Hargreaves, J. R., Kim, J. C., Phetla, G., Watts, C. H. & Porter, J. D. (2008). Is social capital associated with HIV risk in rural South Africa? *Social Science & Medicine, 66,* 1999-2010.

Protopopescu C., Raffi F., Roux P., Reynes J., Dellamonica P., Spire B., Leport C., …& ANRS CO8 APROCO-COPILOTE Study Group. (2009). Factors associated with non-adherence to long-term highly active antiretroviral therapy: a 10 year follow-up analysis with correction for the bias induced by missing data. *Journal of Antimicrobial Chemotherapy, 64,* 599-606.

Puskas, C.M., Forrest, J. I., Parashar, S., Salters, K. A., Cescon A. M., Kaida, A., … Hogg, R. S. (2011). Women and vulnerability to HAART Non-adherence: A literature review of treatment adherence by gender from 2000-2011.

Ryan P. & Sawin K. J. (2009). The Individual and Family Self-Management Theory: Background and perspectives on context, process, and outcomes. *Nursing Outlook,. 57*,217-225.

Simoni, J.M., Frick, P.A., & Huang, B. (2006). A longitudinal evaluation of a social support model of medication adherence among HIV-positive men and women on antiretroviral therapy. *Health Psychology, 25,* 74-81.

Sullivan, P. S., Campsmith, M. L., Nakamura, G. V., Begley, E. B., Schulden, J., & Nakashima, A. K. (2007). Patient and regimen characteristics associated with self-reported nonadherence to antiretroviral therapy. *PLoS One, 2*(6), e552.

Ubbiali, A., Donati, D., Chiorri, C., Bregani, V., Cattaneo, E., Maffei, C., & Visintini, R. (2008). Prediction of adherence to antiretroviral therapy: can patients' gender play some role? An Italian pilot study. *AIDS Care, 20*, 571–575

Vyavaharkar, M., Moneyham, L., Tavakoli, A., Phillips, K. D., Murdaugh, C., Jackson, K., & Meding G. (2007). Social support, coping, and medication adherence among HIV-positive women with depression living in rural areas of the southeastern United States. *AIDS Patient Care STDS, 21*(9), 667-680.

Walsh, J. C., Mandalia, S., & Gazzard, B. G. (2002). Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *Aids, 16*, 269-277.

Wayson Locher, A., Pargament, K., & Duggan, J. (2007). Antiretroviral therapy in the lives of women of colour with HIV. *AIDS Care, 19*, 1048-1051.

Webel, A. R. & Higgins, P. A. (2011). The Relationship Between Social Roles and Self-Management Behavior in Women Living With HIV/AIDS. *Womens Health Issues.* Epub ahead of print.

Webel, A. R., Asher, A., Okonsky, J. G., Cuca, Y., Kaihura, A., Dawson-Rose, C. Hanson, J., & Salata, R. (2011a). *Measuring HIV Self-Management in Women Living with HIV/AIDS: A Psychometric Evaluation Study of the HIV Self-Management Scale.* Manuscript submitted for publication.

Webel A, R. Phillips J. C., Dawson-Rose C., Holzemer W. L., Chen, W. T., Tyer-Viola, L., … & Salata, R. A. (2011b). A Description of Social Capital in Persons Living with HIV/AIDS. Manuscript submitted for publication.

Table 1: Demographic and Clinical Characteristics

Characteristics	**Nonadherent** *Less than 100% in past 3 days* **n=91** **n (%)**
Age: Mean (SD)	46 (8.3)
Race	
African American	59 (67)
White	14 (16)
Hispanic	8 (9)
Other	7 (8)
Education	
11 grade or less	27 (30)
High School Diploma or GED	41 (46)
2 years college	16 (18)
4 yrs/MS/PhD	5 (6)
Marital status	
Married	9 (10)
Single	59 (66)
Separated/divorced	15 (17)
Other	6 (7)
Have children[a]	63 (89)
Currently employed	18 (20)
Permanent housing	74 (82)
HIV medication adherence in past 3 days: Mean (SD)	71 (26.5)
CD4+ T cell count[b]**: cells/mm**^{3} **Median (IQR)**	487 (244-714)
Detectable HIV Viral Load[c] **(> 75 copies/ml)**	20 (33)
Viral Load: Median (IQR)[d]	1720 (412-5100)
Taking a PI based regimen	49 (54)
Ever told had AIDS	46 (52)

a: 78-81% of sample responded
b: 73-85% of sample responded
c: 66-67% of sample responded
d: Of those who had detectable viral loads (n=20)

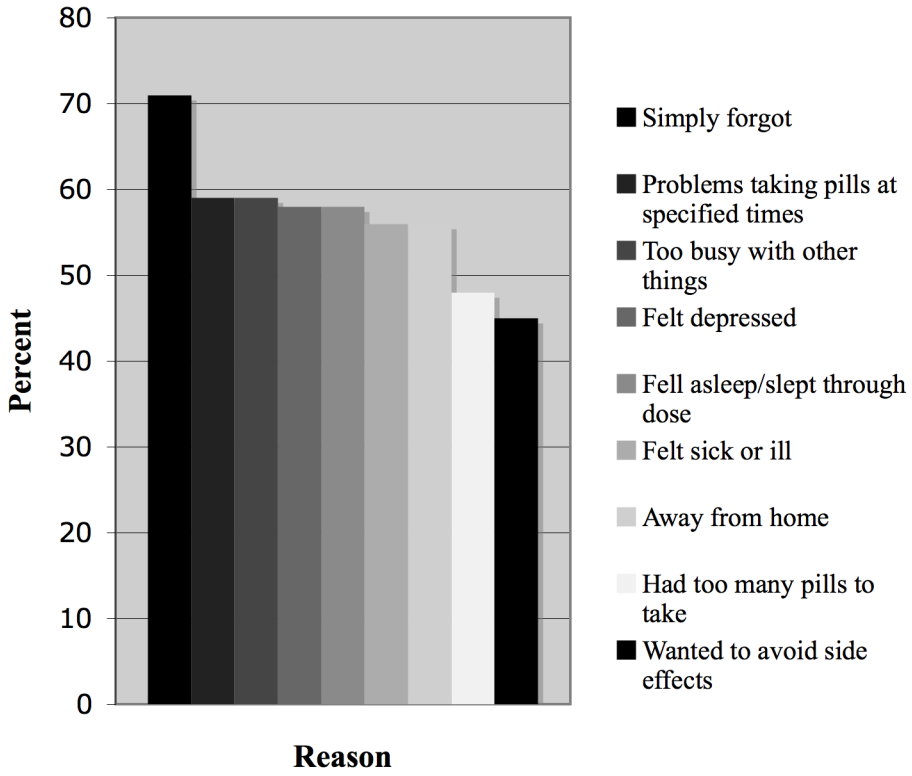
Table 2: Overall Scale Score Summaries

Scale	Mean	SD	Min-Max	Range
Self-reported adherence	71.1	26.53	0-98	0-99
Social capital	2.77	.54	1.15-4.12	0-5
Chronic Disease Self efficacy	6.60	2.13	1-10	1-10
Engagement with Health Care Provider	1.41	.70	.93-3.71	1-4
Access to care[a] a: A score of >36 indicates poor access	21.86	5.46	12-34	0-52

Table 3: Mean adherence by group

Group	Mean adherence	SD	ttest
African American n =59 Other n= 32	69.35 74.34	28.07 23.48	NS
High School or less n= 68 Beyond HS n= 23	71.41 70.21	25.61 29.67	NS
Unemployed n= 70 Employed n= 18	72.81 66.33	26.55 27.41	NS
PI regimen n=49 Non-PI regimen n=42	65.77 77.33	28.84 22.29	p=.03
AIDS diagnosis Yes: n= 46 AIDS diagnosis No: n=42	72.65 69.04	25.58 28.14	NS
Low Social Capital n= 29 High Social Capital n= 62	63.96 74.45	29.66 24.47	NS
Low Chronic Disease Self Efficacy (CDSE) n= 32 High CDSE n= 59	67.21 73.22	26.21 26.68	NS
Low Health Care Provider Engagement (HCP) n= 52 High HCP Engagement n= 39	75.76 64. 89	21.29 31.45	NS p=.06

Figure 1: Reasons for Non-adherence



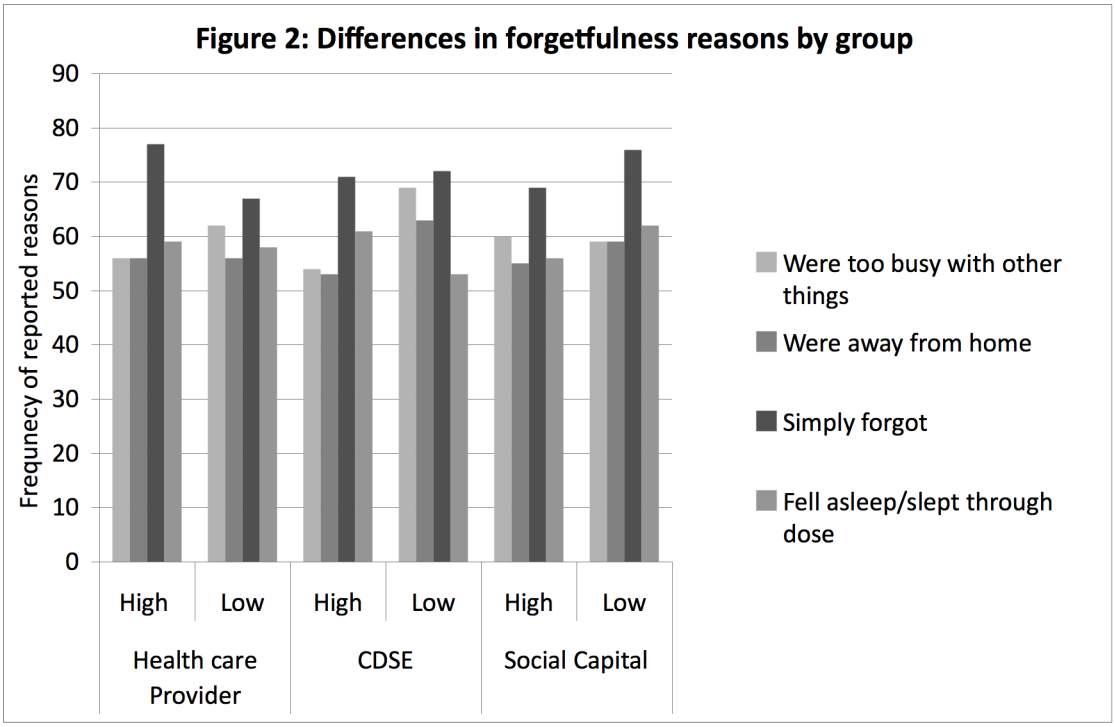


Figure 2: Differences in forgetfulness reasons by group
Frequnecy of reported reasons
90
80
70
60
50
40
30
20
10
0
High
Low
High
Low
High
Low
Health care Provider
CDSE
Social Capital
Were too busy with other things
Were away from home
Simply forgot
Fell asleep/slept through dose

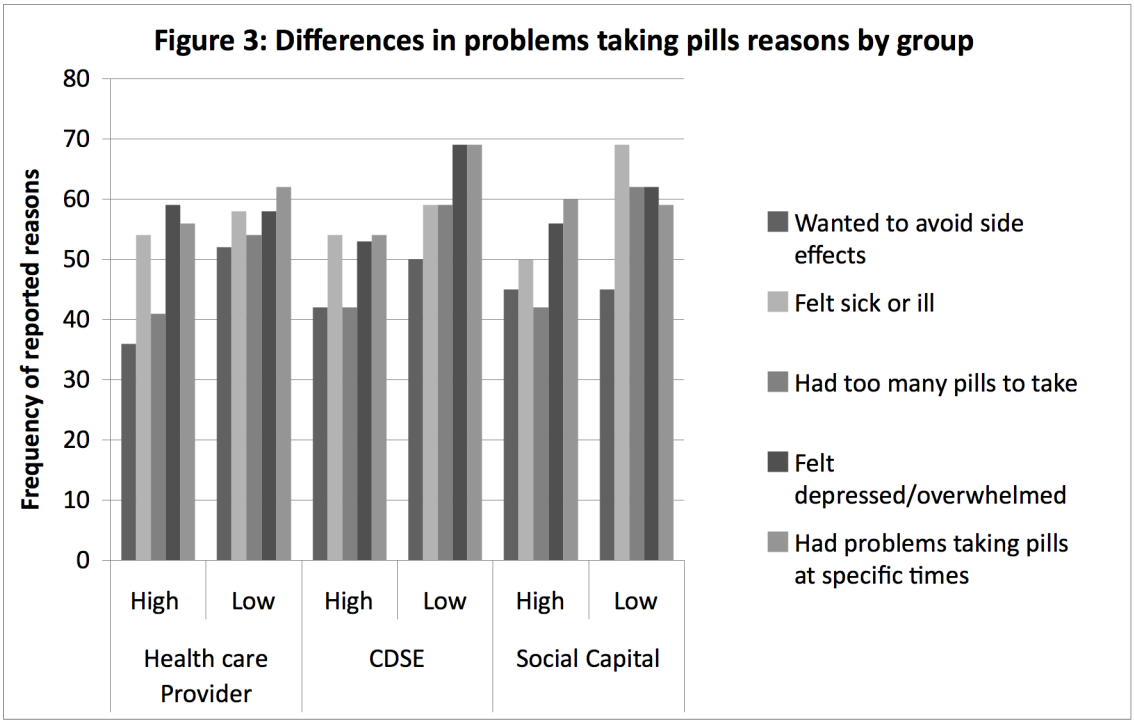


Figure 3: Differences in problems taking pills reasons by group
Frequency of reported reasons
80
70
60
50
40
30
20
10
0
High
Low
High
Low
High
Low
Health care Provider
CDSE
Social Capital
Wanted to avoid side effects
Felt sick or ill
Had too many pills to take
Felt depressed/overwhelmed
Had problems taking pills at specific times

Discussion

The purpose of this dissertation is to examine the reasons why people who are taking antiretroviral therapy are missing their medications and the relationship with documented factors. The goal of the dissertation is to contribute to the scientific literature and provide evidence that can influence a new HIV trajectory of adherence research and intervention development. Three papers are presented that provide their own perspective in which to gain a better understanding of HIV medication adherence behavior using reasons for missed medications as the focus. This dissertation analyzed reasons for non-adherence using an evolutionary approach in order to reach an increased understanding of adherence behavior and introduce a framework that can support translational research. The final chapter of this dissertation will summarize each study's purpose and findings, scientific contribution to the literature, limitations, implications for future research, as well as provide suggestions for rethinking the trajectory of HIV adherence for nursing research.

The first paper, *Problems taking pills: Understanding HIV medication adherence from a new perspective,* examines several key correlates of reasons for missed medication in a diverse sample of people living with HIV/AIDS (PLWHA) from nine cities in the United States using an ordinal regression model. Regimen type, symptom experience, AIDS diagnosis, other health conditions, and social support offer a common profile of PLWHA and complements the existing literature. The ACTGrev Reasons for Missed Medications scale has two factors. Five reasons group into problems taking pills and four reasons group into forgetfulness. In this study, problems taking pills was associated with the use of a PI regimen and forgetfulness was not. In this sample, a person taking a PI

based regimen has a 70% increase in problems taking pills. Persons who have an increase in symptom experience are approximately four times more likely to have problems taking pills and persons in this sample with other health conditions are 30% less likely to have problems taking pills. In this sample, social support and AIDS were not associated with problems taking pills.

In the second paper, *Not Just Simply Forgetting: Appreciating Reasons for Missed Medications in Women by Adherence Level and Regimen*, the purpose is to examine and gain an appreciation of the reasons why women living with HIV and AIDS taking ART, in Cleveland, OH and the San Francisco Bay Area of California are missing their HIV medications, and how the results can influence an alternate approach to adherence discussions. In this sample, women were 2.2 times more likely to document reasons grouped into forgetfulness than grouped into problems taking pills (ACTGrev scale used). The dominant reason was that people simply forgot. There was a difference between the adherent and nonadherent groups in reasons for missed medications given overall, but no difference between those on a PI based versus a non-PI based regimen. In this sample of women, similar results regarding forgetfulness are consistent with the research over the last decade. These results when scrutinized using a big picture format within the body of research possibly points to a possible complacency on how providers engage and address adherence discussions, specifically in response to 'simply forgot' as a main reason for non-adherence (Barfod, Hecht, Rubow & Gerstoft, 2006). If the reminder devices, reminder strategies and interventions are not increasing adherence levels in a sustainable way and forgetfulness remains a leading reason, perhaps a new trajectory is needed. Appreciating the type of adherence (intentional vs. unintentional), and a more

focused adherence discussion with the patient are possible avenues. A patient-centered approach that reviews types of reasons, frequency of reasons and type of non-adherence (intentional vs. unintentional) can support development of novel interventions.

The final paper in this dissertation, *Understanding Reasons for Non-Adherence in Women Living with HIV and AIDS Using a Self-Management Framework*, explores reasons for non-adherence, and the influence of selected contextual, process and outcome variables. This sample assessed HIV-infected women, primarily African American from two cities in the US who reported missing a dose of medication in the past three days. Demographic and clinical characteristics (race, education, employment, regimen, AIDS diagnosis), access to care and social capital are grouped into contextual factors. Chronic disease self-efficacy is a process factor and the outcome factors identified are the level of engagement with health care provider and adherence. The many contextual, process and outcome factors are organized using a self-management framework to support the dynamic nature of adherence. In this sample of nonadherent women (self-report of less than 100% in past three days) the mean adherence level is 71% and the mean number of reasons (out of nine) documented for missing medication is five. The most frequent reason documented was simply forgot and the least common was wanted to avoid side effects. Frequency of reasons does not consistently match with adherence level (i.e. greater frequency of reasons did not mean less adherence). Overall, the two reasons differed between groups. African American women reported wanting to avoid side effects at a significantly higher proportion than women of other races, and women who were not employed reported away from home at a significantly higher proportion than those employed.

Contributions

Each paper presented has its own unique contribution and taken together coalesce to suggest a new trajectory for HIV adherence. The first paper, *Problems taking pills: Understanding HIV medication adherence from a new perspective* analyzes reasons for missed medications using the ACTGrev scale in association with factors and uses an ordinal regression model. Analyzing the reasons using the ordinal regression model has not been done with reasons for missed medications. Utilizing all of the information on the ordinal scale rather than dichotomizing is a strength in the analysis plan. The proportional odds ratio offers a useful and translatable finding. The findings of the study regarding PI regimens and symptom experience reinforce the existing literature. Additionally, coupled with the existing literature, it may provide the health care provider with a proactive lens when discussing adherence with patients. For example, a patient who may be complaining of an increase in any type of symptoms, is depressed and on a PI based regimen will most likely have increased problems taking their HIV medication. Understanding this perspective and bringing in the evidence can support the patient-provider communication regarding specific areas to target for adherence discussions. Additionally, the finding on multiple health conditions in this study being supportive of adherence is interesting and important to explore in terms of HIV being a chronic disease and how it fits into the overall picture. Lastly, the insignificant results related to social support provide an interesting dynamic. Although this study did not document a clinical scale for depression, it did report depression in the symptom scale, and was listed in the top five symptoms. To this end, the finding on social support is not unexpected in that

depression is known to disrupt social support systems. Nevertheless, bringing together this information can be complicated. This study's findings demonstrates the complex nature of not only adherence behavior but overall management of health, thus highlighting the need for a dynamic framework that takes into account the dynamic nature of life overall.

The second paper *Not Just Simply Forgetting: Appreciating Reasons for Missed Medication in Women by Adherence Level and Regimen*, contributes to the growing literature on women and HIV. The overall finding that women in the sample are 2.2 times more likely to document forgetfulness type reasons is consistent with overall adherence reasons literature. Unfortunately, after over a decade of research focused on reminder devices, strategies and interventions, the literature continues to report forgetfulness as a leading reason for non-adherence. The contribution of this study highlights the need for gaining an appreciation for what forgetfulness means. Perhaps the patient-provider communication needs to engage the patients more about what forgetting actually means. The key contributions of this study are that it reinforces the existing literature that forgetfulness is still a problem, it complements the existing research in regard to expanding the information specific to reasons, and focuses on women. The value of this study is that the findings illustrate the need to engage the individual patient more fully about their adherence behavior. Communication around what was happening when they forgot, was it intentional vs. unintentional. The few studies that have specifically observed and examined HIV provider interactions in regard to adherence discussions reported communication to be the main difficulty, often a directive approach was used,

and the dialogue often lacked problem solving (Barfod, Hecht, Rubow & Gerstoft, 2006; Wilson et al., 2010).

The final paper, *Understanding Reasons for Non-adherence in Women Living with HIV and AIDS using a Self-Management Framework,* identified a framework not yet used to view HIV adherence research or HIV adherence interventions. This study organized the many factors associated with the adherence literature using the self-management framework. Although the study only begins to touch on the integration of using a self-management framework, it provides the foundation for future research. The findings provide a platform that expands the concept of social capital with women living with HIV and AIDS and adherence. Additionally, the focus on reasons for missed medication demonstrates that reasons are often discrete, and this supports the idea that not only is adherence a dynamic phenomenon but managing one's overall health is also dynamic. This study has helped demonstrate the need for interventions to focus on flexibility that allows for adaptation to individuals unique adherence barriers.

The coalescing of the first two papers within the existing body of research illuminated the need to rethink the adherence trajectory. A new framework is suggested to view adherence that can possibly adapt not only to the dynamic nature of adherence, but also to the dynamic nature of life.

Limitations

Limitations are inherent in all studies and an awareness of the specific limitations noted in this dissertation will allow for an open review when evaluating the results and will identify areas of improvement for future research. Overall, the limitation noted

throughout all three studies is the use of self-report. Although self-reporting on adherence has been validated in the literature (Nieuwkert & OOrt, 2005; Simoni et al., 2006) and is the most commonly used adherence measure (due to its efficiency and cost effectiveness), it is subject to social desirability and recall bias. The use of the ACTGrev scale is not only limited in its self-report nature but is restricted in regard to only allowing participants to select from nine reasons without providing a space for other. Although the construct of adherence has been validated in this scale, it does not provide the whole picture.

The main limitation in the first paper is the lack of a quantitative measure of adherence. The study data was conducted as a secondary analysis, which can also be viewed as a limitation. The ACTGrev Reasons for Missed Medication scale was used as a proxy for adherence and does not represent a precise measurement. The background of the participants in regard to number of years taking ART, years having HIV and regimen specifics, narrowed the profile of the participants and could have been included as independent variables to strengthen the findings. In addition, the social support measure provided only a one-dimensional perspective. The inability for the researcher and participant to be clear on the definition allows for inaccuracy. This coupled with the cross sectional design restricts the finding. Furthermore, the exclusion criteria of symptom free in the last week, has implications for the generalizability for the study.

The data from the second and third paper were obtained from the same study sample, thus share some common limitations. The use of a 3-day visual analogue scale (VAS) without additional measures of self-report (i.e. 30-day VAS; 3 day recall of percent of doses taken/prescribed) and an objective measure of adherence limits the

construct validity of these studies. The data collected on viral load was self-report and not confirmed with medical records for the entire sample; only a portion of the sample's viral load was taken from chart abstraction. The study data did not capture specific information surrounding regimen history, depression, alcohol use, methadone, and substance abuse. This information has been demonstrated to affect adherence and could possibly identify patterns of adherence not addressed. Additionally, information surrounding adherence strategies and specific communication patterns regarding adherence with providers was not explored. Furthermore, the women in this sample were from two cities in the US who attend HIV specialty clinics, limiting the generalizability.

The third paper dichotomized the scales measuring social capital, chronic disease self-efficacy and engagement with the health care provider. Generally, dichotomizing discards useful information and other statistical issues can arise (power is lost and a reduction in the variance accounted for). These limitations should be addressed in future research.

Implication for future research

Overall and individually, the threes studies that comprise this dissertation have implications for future research. The first paper addresses the categorization of reasons (problems taking pills vs. forgetfulness) in a way that has not been studied before and offers a platform to continue developing that may result in a proactive algorithm type reference for providers. A reference may assist providers to intervene early when potential red flags are raised through communication from the patients. However, before a reference is established additional research focused using this perspective, (ordinal

regression model and types of reasons) is needed. Additional factors (i.e. depression, alcohol use) need to be examined using this method. Suggestions on how to improve on this research are documented in the limitations and should be carefully considered.

Suggestions from the second paper in regard to future research can be split into two focus areas. The first can be focused on additional data to collect (i.e. depression, substance use, other roles they see themselves having, regimen complexity) in order to provide a more complete picture of women living with HIV and AIDS. The second can concentrate on reasons for missed medication. The limitation of the ACTGrev scale does not distinguish between intentional and unintentional adherence or utilize the qualitative data published on adherence themes. Although scales have been validated that capture reasons for missed medication, improvement in this area is needed. Furthermore, this study has exposed the need to continue with research that captures what the current adherence communication/counseling practices are in clinics, offices and support organizations.

Finally, the third paper introduces self-management as a framework to organize adherence research. Building upon this framework, as a guide to inform adherence strategies and intervention development is a clear next step. A more robust study needs to be completed inclusive of the various concepts included in the framework. Lessons learned and the experiences from the other disciplines that have used self-management need to be investigated (Barlow, Wright, Sheasby, Turner & Hainsworth, 2002). Additionally, seeking collaboration with researchers who have integrated components of self-management in order to respond to symptomatic HIV will provide insight into the use of a self-management framework (Gifford, Laurent, Gonzales, Chesney, Lorig, 1998;

Webel, 2010). Building upon this idea of self-management to support adherence and what that means for the patient-provider relationship and the multiple roles patients are engaged in are essential. Continuing to explore how best to translate this information on an individual and clinic level is fundamental.

Way Forward: Rethinking the Trajectory

As we enter the third decade of the HIV and AIDS epidemic it is critical that we reflect upon the extraordinary research that has been conducted thus far, align it with the knowledge of the individual experience, and rethink the trajectory of HIV nursing research.

The published literature on HIV adherence research is vast. The scientific community has researched factors that hinder and support adherence (Ammassari et al., 2002; Atkinson & Petrozzino, 2009; Barfod, Sorensen, Nielsen, Rodkjaer & Obel, 2006; Catz, Kelly, Bogart, Benotsch & McAuliffe, 2000; Chesney et al., 2000; Deloria-Knoll et al.,, 2004; Heckman, Catz, Heckman, Miller & Kalichman, 2004; Kyser et al., 2011; Protopopescu et al., 2009; Ramirez Garcia & Cote, 2003; Sullivan et al., 2007). Systematic reviews, empirical reviews and meta-analysis synthesize factors that are consistently associated with adherence, the factors, which are inconsistently associated, and those factors those are generally not (Atkinson & Petrozzino, 2009; Ortego et al., 2011; Puskas et al., 2011). Decades of this research has given the research community a wealth of information to utilize when developing adherence interventions, and several reviews of interventions have also been conducted (Amico, Harman, & Johnson 2006; Cote & Godin, 2005; Fogarty et al., 2002; Ickovics & Meade, 2002; Simoni, Frick,

Pantalone & Turner, 2003; Simoni, Pearson, Pantalone, Marks & Crepaz, 2006; Rueda et al., 2006; Saberi & Johnson, 2011; Sandelowski, Voils, Chang, & Lee, 2009). The research community has highlighted that only a small proportion of intervention studies meet acceptable levels of scientific rigor, the efficacious interventions for improving adherence are not simple, the magnitude of improvement is often small and the focus on targeting subgroups has not been successful. Recent suggestions and approaches include a patient-centered care approach, understanding types of adherence (intentional vs. unintentional), the integration of adult learning principles, and individually tailored, multi-function technologies coupled with health care provider communication (Wilson, 2009; Saberi & Johnson, 2011).

The findings from this dissertation support the steps: observe, listen and investigate. The research conducted has provided evidence to rethink the trajectory and focus on the individual. Many of the overall results from this dissertation parallel the existing research, the focus on reasons for missed medication and their intersection with documented factors highlights the dynamic nature of the reasons and the individual, which supports the recent suggestions in the literature, and the idea of rethinking the trajectory. In order to support this rethinking, a shift in the conduct of research may need to happen. One critical shift is to observe, listen and investigate at the center of adherence discussions (at the individual's community) and explore what interventions are feasible, flexible, and adaptable and take into consideration the individual and their unique barriers. Three decades of research has provided the scientific community with a strong building block, the researchers have strived to bring the research to the community, but as nurse researchers we can utilize the lessons learned and now bring the community and the

individual to the research. As nurses and researchers assisting patient in taking their medication optimally, the one to one interaction needs to be enhanced in order to process the specific reasons for non-adherence. Improvement in assessing the emotional reasons as well as the practical day-to-day barriers is part and parcel of not only a patient-centered approach but also self-management. And this needs to be observed, listened and investigated at the individual's community. Developing a HIV adherence nursing research agenda that begins at the individual and community level is a critical step in third decade of the HIV adherence trajectory.

Conclusion

This dissertation provides information to support a better understanding into people who are missing their HIV medications and the association with documented factors affecting adherence. This dissertation contributes to the scientific literature and provides evidence that influences a rethinking of the HIV adherence trajectory. The evolution of these three studies suggests individual strategies that are parts of the whole. Translating the evidence of a common profile of non-adherence into a proactive individual discussion, engaging the patient-provider relationship to appreciate the reason for intentional or unintentional non-adherence, offering a self-management framework to organize the discussion and intervention development, and shifting the focus of adherence research to the individual's community are the evolutionary steps that can potentially create a fluid response for people living with HIV and AIDS to reach optimal levels of adherence.

Nonetheless, this dissertation identified several limitations and future research with reasons for missed medication needs to consider multiple adherence measurement tools and the importance of capturing reasons in a more comprehensive manner. HIV adherence in women is a vital component to adherence research and particularly relevant in regard to the dynamic nature of the many family and social roles for which they are responsible. Bridging quantitative and qualitative adherence research can offer a holistic view of the vast body of literature and support the increased understanding of adherence.

If these suggestions are put into action a better understanding of the dynamics of adherence behavior can be achieved and would make possible the development of strategies and interventions that are accessible, appropriate, flexible and feasible to support persons taking antiretroviral therapy. This dissertation has started to bridge the gap between the reasons for non-adherence and a translatable framework to support optimal adherence within the dynamic phenomenon of adherence.

References

Amico, K. R., Harman, J. J., & Johnson, B. T. (2006). Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996 to 2004. *Journal of Acquired Immune Deficiency Syndromes, 41*, 285-297.

Amico, R., Konkle-Parker, D., Cornman, H., Barta, W., Ferrer, R., Norton, W. E., ... Fisher, W. A. (2007). Reasons for ART non-adherence in the Deep South: Adherence needs of a sample of HIV-positive patients in Mississippi. *AIDS Care, 19*, 1210-1218.

Ammassari, A., Trotta, M. P., Murri, R., Castelli, F., Narciso, P., Noto, P.,…AdiCoNA Study Group. (2002). Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *Journal of Acquired Immune Deficiency Syndromes, 31 Suppl 3*, S123-127.

Arnsten, J. H., Demas, P. A., Grant, R. W., Gourevitch, M. N., Farzadegan, H., Howard, A. A., I Schoenbaum, E. E. (2002). Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *Journal of General Internal Medicine, 17*, 377-381.

Atkinson, M.J. & Petrozzino, J.J. (2009). An evidence-based review of treatment-related determinants of patients' Nonadherence to HIV medications. *AIDS Patient Care and STDs, 23,* 90-914.

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

Bangsberg, D. R., Hecht, F.M., Clague, H., Charlebois,E. D., Ciccarone, D., Chesney, M., & Moss, A. (2001). Provider assessment of adherence to HIV antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes, 26*, 435-442.

Barfod, T. S., Hecht, F. M., Rubow, C., & Gerstoft, J. (2006). Physician's communication with patients about adherence to HIV medication in San Francisco and Copenhagen: a qualitative study using Grounded Theory. *BMC Health Services Research, 4,* 154.

Barfod, T. S., Sorensen, H. T., Nielsen, H., Rodkjaer, L., & Obel, N. (2006). 'Simply forgot' is the most frequently stated reason for missed doses of HAART irrespective of degree of adherence. *HIV Medicine, 7*, 285-290.

Barlow, J., Wright, C., Sheasby, J., Turner, A., & Hainsworth, J. (2002). Self-management approaches for people with chronic conditions: a review. *Patient Education Counseling, 48*, 177-187.

Beusterien, K.M., Davis, E. A., Flood, R., Howard, K., & Jordan. J. (2008). HIV patient insights on adhering to medication: a qualitative analysis. *AIDS Care, 20*, 244-252.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology, 19*, 124-133.

Chesney, M. A., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J., Zwickl, B., et al. (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care, 12*, 255-266.

Chesney, M. (2003). Adherence to HAART regimens. *AIDS Patient Care STDS, 17*, 169-177.

Centers for Disease Control and Prevention. (2011a). *National Women and Girls Awareness Day.* Retrieved September 10, 2011 from http://www.cdc.gov/features/womengirlshivaids/

Centers for Disease Control and Prevention. (2011b). *Chronic Disease Prevention and Health Promotion.* Retrieved September 10, 2011 from http://www.cdc.gov/chronicdisease/overview/index.htm#ref2

Clavel, F., & Hance, A. J. (2004). HIV drug resistance. *New England Journal of Medicine, 350,* 1023-1035.

Crane, J. T., Kawuma, A., Oyugi, J. H., Byakika, J. T., Moss, A., Bourgois, P., & Bangsberg, D. (2006). The price of adherence: qualitative findings from HIV positive individuals purchasing fixed-dose combination generic HIV antiretroviral therapy in Kampala, Uganda. *AIDS Behavior, 10*, 437-442.

Cote, J. K., & Godin, G. (2005). Efficacy of interventions in improving adherence to antiretroviral therapy. *International Journal of STD and AIDS, 16*, 335-343.

Deloria-Knoll, M., Chmiel, J. S., Moorman, A. C., Wood, K. C., Holmberg, S. D., & Palella, F. J. (2004). Factors related to and consequences of adherence to antiretroviral therapy in an ambulatory HIV-infected patient cohort. *AIDS Patient Care STDS, 18*, 721-727.

Ferguson, T.F., Stewart.K.E., Funkhouser, E., Tolson, J., Westfall, A.O., & Saag, M.S. (2002). Patient-perceived barriers to antiretroviral adherence: Associations with race. *AIDS Care, 14*, 607-617.

Fogarty, L., Roter, D., Larson, S., Burke, J., Gillespie, J., & Levy, R. (2002). Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Education and Counseling, 46*, 93-108.

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

Gifford, A. L., Laurent, D. D., Gonzales, V. M., Chesney, M. A., & Lorig, K. R. (1998). Pilot randomized trial of education to improve self-management skills of men with symptomatic HIV/AIDS. *Journal of Acquired Immune Deficiency Syndromes, 18*, 136-144.

Gill, C. J., Hamer, D. H., Simon, J. L., Thea, D. M., & Sabin, L. L. (2005). No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa. *AIDS, 19*, 1243-1249.

Hardy, M.C. (1948). Follow-up of medical recommendations. *Journal of the American Medical Association, 136,* 20-27.

Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P., & Yao, X. (2008). Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*(2), CD000011.

Heckman, B. D., Catz, S. L., Heckman, T. G., Miller, J. G., & Kalichman, S. C. (2004). Adherence to antiretroviral therapy in rural persons living with HIV disease in the United States. *AIDS Care, 16*, 219-230.

Holtgrave, D. R., & Pinkerton, S. D. (1997). Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology,, 16*, 54-62.

Holstad, M. M., Diiorio, C., & McCarty, F. Adherence, sexual risk, and viral load in HIV-infected women prescribed antiretroviral therapy. *AIDS Patient Care STDS, 25*, 431-438.

Howard, A. A., Arnsten, J.H., Lo, Y., Vlahov, D., Rich, J. D.,… HER Study Group. (2002). A prospective study of adherence and viral load in a large mulit-center cohort of HIV-infected women. *AIDS, 16,* 2175-2182.

Ickovics, J. R., & Meade, C. S. (2002). Adherence to antiretroviral therapy among patients with HIV: a critical link between behavioral and biomedical sciences. *Journal of Acquired Immune Deficiency Syndromes, 31 Suppl 3*, S98-102.

Jones, D.L., Ishii, M., LaPerriere A., Stanley H., Antoni, M., Ironson, G., … Weiss, S. M. (2003). *AIDS Care, 15,* 463-474.

Kalichman, S.C., Catz, S., & Ramachandran, B. S.(1999). Barriers to HIV/AIDS treatment and treatment adherence among African-American adults with disadvantaged education. *Journal of the National Medical Association, 91*, 439-446.

Knowlton, A. R., Yang, C., Bohnert, A., Wissow, L., Chander, G., & Arnsten, J. A. (2011). Main partner factors associated with worse adherence to HAART among women in Baltimore, Maryland: a preliminary study. *AIDS Care, 23*, 1102-1110.

Konkle-Parker, D. J., Erlen, J. A., & Dubbert, P. M. (2008). Barriers and facilitators to medication adherence in a southern minority population with HIV disease. *Journal of the Association of Nurses in AIDS Care, 19*, 98-104.

Kremer, H., Ironson, G., & Porr, M. (2009). Spiritual and mind-body beliefs as barriers and motivators to HIV-treatment decision-making and medication adherence? A qualitative study. *AIDS Patient Care STDS, 23*, 127-134.

Kyser, M., Buchacz, K., Bush, T. J., Conley, L. J., Hammer, J., Henry, K., … Brooks, J. T. (2011). Factors associated with non-adherence to antiretroviral therapy in the SUN study. *AIDS Care, 23*, 601-611.

Little, S. J., Holte, S., Routy, J. P., Daar, E. S., Markowitz, M., Collier, A. C., …Richman, D.D. (2002). Antiretroviral-drug resistance among patients recently infected with HIV. *New England Journal of Medicine, 347*, 385-394.

Lewis, M. P., Colbert, A., Erlen, J., & Meyers, M. (2006). A qualitative study of persons who are 100% adherent to antiretroviral therapy. *AIDS Care, 18*, 140-148.

Lopez, E. J., Jones, D. L., Villar-Loubet, O. M., Arheart, K. L., & Weiss, S. M. (2010). Violence, coping, and consistent medication adherence in HIV-positive couples. *AIDS Education and Prevention, 22*, 61-68.

Low-Beer, S., Yip, B., O'Shaughnessy, M. V., Hogg, R. S., & Montaner, J. S. (2000). Adherence to triple therapy and viral load response. *Journal of Acquired Immune Deficiency Syndromes, 23*, 360-361.

Maggiolo, F., Ravasio, L., Ripamonti, D., Gregis, G., Quinzan, G., Arici, C., Airoidi, M., & Suter, F. (2005). Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. *Clinical Infectious Diseases,40*, 158-163.

Meyer, J. P., Springer, S. A., & Altice, F. L. (2011). Substance abuse, violence, and HIV in women: a literature review of the syndemic. *Journal of Womens Health (Larchmt), 20*, 991-1006.

Mills, E. J., Nachega, J. B., Buchan, I., Orbinski, J., Attaran, A., Singh, S.,… Bangsberg, D. (2006). Adherence to Antiretroviral Therapy in Sub-Saharan Africa and North America: A Meta-analysis. *Journal of the American Medical Association, 296*, 679-690.

Mohammadpour, A., Yekta, Z. P., & Nikbakht Nasrabadi, A. R. (2010). HIV-infected patients' adherence to highly active antiretroviral therapy: a phenomenological study. *Nursing Health Sciences, 12*, 464-469.

Murphy, D. A., Greenwell S., Hoffman,D. (2002). Factors Associated with Antiretroviral Adherence Among HIV-Infected Women with Children, *Women & Health, 36,* 97-111.

Nieuwkert, P. T., & Oort, F. J. (2005). Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: A meta-analysis. *Journal of Acquired Immune Deficiency Syndromes, 38*, 445-448.

Okonsky, J. G. (2011). Problems taking pills: understanding HIV medication adherence from a new perspective. *AIDS Care*. Epub.

Ortego, C., Huedo-Medine, T. B., Llorca, J., Sevilla, Santos, P., Rodriguez, E., Warren, M. R., & Vejo, J. (2011). Adherence to highly active antiretrovial therapy (HAART): A meta-analysis. *AIDS and Behavior, 15,* 1381-1396.

Oyugi, J. H., Byakika-Tusiime, J., Charlebois, E., Kityo, C., Mugerwa, R., & Mugyenyi, P., & Bangsberg D. (2004). Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *Journal of Acquired Immune Deficiency Syndromes, 36*, 1100-1102.

Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., Wagener, M.M., & Singh.N. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine, 133*, 21-30.

Phillips, A. N., Neaton, J., & Lundgren, J. D. (2008). The role of HIV in serious diseases other than AIDS. *AIDS, 22*, 2409-2418.

Protopopescu, C., Raffi, F., Roux, P., Reynes, J., Dellamonica, P., Spire, B., et al. (2009). Factors associated with non-adherence to long-term highly active antiretroviral therapy: a 10 year follow-up analysis with correction for the bias induced by missing data. *Journal of Antimicrobial Chemotherapy, 64*, 599-606.

Puskas, C.M., Forrest, J. I., Parashar, S., Salters, K. A., Cescon A. M., Kaida, A., … Hogg, R. S. (2011). Women and vulnerability to HAART Non-adherence: A literature review of treatment adherence by gender from 2000-2011. *Current HIV/AID Report, 8*, 277-287.

Ramirez Garcia, P., & Cote, J. K. (2003). Factors affecting adherence to antiretroviral therapy in people living with HIV/AIDS. *Journal of the Association of Nurses in AIDS Care, 14*, 37-45.

Roberts, K. J., & Mann, T. (2003). Adherence to antiretroviral medications in HIV/AIDS care: a narrative exploration of one woman's foray into intentional non-adherence. *Health Care for Women International, 24*, 552-564.

Rochon, D., Ross, M. W., Looney, C., Nepal, V.P., Price, A. J., & Giordano, T. P. (2011). Communication strategies to improve HIV treatment adherence. *Health Communication, 26*, 461-467.

Remien, R. H., Hirky, A. E., Johnson, M. O., Weinhardt, L. S., Whittier, D., & Le, G. M. (2003). Adherence to medication treatment: a qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities. *AIDS and Behavior, 7*, 61-72.

Rueda, S., Park-Wyllie, L. Y., Bayoumi, A. M., Tynan, A. M., Antoniou, T. A., Rourke, S. B., et al. (2006). Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. *Cochrane Database Systematic Review, 3*, CD001442.

Ryan P. & Sawin K. J. (2009). The Individual and Family Self-Management Theory: Background and perspectives on context, process, and outcomes. *Nursing Outlook,. 57*, 217-225.

Saberi, P. & Johnson, M. O. (2011). Technology-based self-care methods of improving antiretroviral adherence: a systematic review. *PLoS One, 6*, e27533.

Saha, S., Beach, M.C., & Cooper, L. A. (2008). Patient centeredness, cultural competence and healthcare quality. *Journal of the National Medical Association, 100*, 1275-1285.

Sandelowski, M., Voils, C. I., Chang, Y., & Lee, E. J. (2009). A systematic review comparing antiretroviral adherence descriptive and intervention studies conducted in the USA. *AIDS Care, 21*, 953-966.

Sankar, A., Golin, C., Simoni, J. M., Luborsky, M., & Pearson, C. (2006). How qualitative methods contribute to understanding combination antiretroviral therapy adherence. *Journal of Acquired Immune Deficiency Syndromes, 43 Suppl 1*, S54-68.

Sax, P. E., Meyers, J., Mugaver, M., & Davis, K. L. (2010). Adherence to antiretroviral treatment regimens and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *Journal of International AIDS Society, 13, Suppl 4*: 03.

Stevens, W., Kaye, S., & Corrah, T. (2004). Antiretroviral therapy in Africa. *British Medical Journal, 328*, 280-282.

Simoni, J. M., Frick, P. A., Pantalone, D. W., & Turner, B. J. (2003). Antiretroviral adherence interventions: a review of current literature and ongoing studies. *Topics in HIV Medicine, 11*, 185-198.

Simoni, J. M., Pearson, C. R., Pantalone, D. W., Marks, G., & Crepaz, N. (2006). Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. *Journal of Acquired Immune Deficiency Syndromes, 43 Suppl 1*, S23-35.

Stevens, P. E., & Hildebrandt, E. (2009). Pill taking from the perspective of HIV-Infected women who are vulnerable to antiretroviral treatment failure. *Qualitative Health Research, 19*, 593-604.

Sullivan, P. S., Campsmith, M. L., Nakamura, G. V., Begley, E. B., Schulden, J., & Nakashima, A. K. (2007). Patient and regimen characteristics associated with self-reported nonadherence to antiretroviral therapy. *PLoS One, 2*, e552.

Ubbiali, A., Donati, D., Chiorri, C., Bregani, V., Cattaneo, E., Maffei, C., & Visintini, R. (2008). Prediction of adherence to antiretroviral therapy: can patients' gender play some role? An Italian pilot study. *AIDS Care, 20*, 571–575

United States Department of Health and Human Services. (2011a). *Timeline/History.* Retrieved September 30, 2011 from http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm117935.htm

United States Department of Health and Human Services, Food and Drug Administration, FDA Approved HIV AIDS Drugs. (2011b). *Drugs used in the treatment of HIV*

infection. Retrieved September 30, 2011, from http://www.fda.gov/oashi/aids/virals.html

Vyavaharkar, M., Moneyham, L., Tavakoli, A., Phillips, K. D., Murdaugh, C., Jackson, K., & Meding, G. (2007). Social support, coping, and medication adherence among HIV-positive women with depression living in rural areas of the Southeastern United States. *AIDS Patient Care and STDs, 21*, 667-680.

Walsh, J. C., Horne, R., Dalton, M., Burgess, A. P., & Gazzard, B. G. (2001). Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care, 13*, 709-720.

Wayson Locher, A., Pargament, K., & Duggan, J. (2007). Antiretroviral therapy in the lives of women of colour with HIV. *AIDS Care, 19*, 1048-1051.

Webel, A. R. Testing a peer-based symptom management intervention for women living with HIV/AIDS. *AIDS Care, 22*, 1029-1040.

Webel, A. R. & Higgins, P. A. (2011). The Relationship Between Social Roles and Self-Management Behavior in Women Living With HIV/AIDS. *Womens Health Issues.* Epub ahead of print.

Wilson, I. B. (2010). Improving treatment adherence. *John Hopkins Advanced Studies in Medicine, 10,* 53-57.

Wood, E., Hogg, R. S., Yip, B., Harrigan, P. R., O'Shaughnessy, M. V., & Montaner, J. S. (2004). The impact of adherence on CD4 cell count responses among HI-infected patients. *Journal of Acquired Immune Deficiency Syndromes, 35,* 261-268.

Yard, S. S., Huh, D., King, K. M., & Simoni, J. M. (2011). Patient-Level Moderators of the Efficacy of Peer Support and Pager Reminder Interventions to Promote Antiretroviral Adherence. *AIDS and Behavior*. Epub.

Publishing Agreement

It is the policy of the University to encourage the distribution of all theses, dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and manuscripts will be routed to the library via the Graduate Division. The library will make all theses, dissertations, and manuscripts accessible to the public and will preserve these to the best of their abilities, in perpetuity.

Please sign the following statement:

I hereby grant permission to the Graduate Division of the University of California, San Francisco to release copies of my thesis, dissertation, or manuscript to the Campus Library to provide access and preservation, in whole or in part, in perpetuity.

Author Signature

12/20/2011

Date