FACTORS ASSOCIATED WITH POOR HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) MEDICATION ADHERENCE AMONG OLDER ADULTS LIVING WITH HIV IN THE U.S.

by

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A dissertation submitted to the faculty of
The University of North Carolina at Charlotte
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in
Health Services Research

Charlotte

2016

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ABSTRACT

BRIAN WITT. Factors associated with poor highly active antiretroviral therapy (HAART) medication adherence among older adults living with HIV in the U.S. (Under the direction of DR. LARISSA R. BRUNNER HUBER)

Background: In the U.S., the number of individuals living with HIV aged 50 years and older has been consistently increasing. Using Centers for Disease Control and Prevention epidemiological data, researchers estimated that in 2015, more than half of the individuals living with HIV in the U.S. were over the age of 50. Optimal adherence to HIV treatment regimens can greatly reduce morbidity and mortality among this population, as well as reduce the risk of transmission of the virus to others. Few studies have examined the association between behavioral and psychological characteristics and HIV medication adherence among an older population.

Objective: This study evaluated the association between adherence and the following patient-reported outcomes: hazardous alcohol use, substance use, depression, quality of life, symptom burden, and physical activity level.

Methods: Using data from the Centers for AIDS Research's Network of Integrated Clinical Systems (CNICS) project, a cross-sectional study was performed among 3,309 patients age 50 and older from seven different clinics in urban centers across the U.S. Exposure and outcome data were self-reported and collected through reliable and valid survey tools. Logistic regression analyses were conducted to explore relationships between each of the patient-reported outcomes and medication adherence. Multivariate logistic regression models were used to estimate odds ratios (ORs) and 95% confidence

intervals (CIs), controlling for race/ethnicity, gender, age, clinic site, chronic illness comorbidity, and risk category.

Results: There were statistically significant associations between all of the patient reported outcomes and adherence, with the one exception of physical activity level. Hazardous alcohol drinkers and current substance users had increased odds of poor adherence (OR=1.50; 95% CI: 1.24-1.82 and OR=3.83; 95% CI: 2.96-4.97, respectively). Patients with mild or severe depressive symptoms had almost 60% increased odds of poor adherence (OR=1.58; 95% CI: 1.30-1.93 and OR=1.56; 95% CI: 1.05-2.32, respectively), and patients with moderate depressive symptoms had more than twice the odds of poor adherence (OR=2.28; 95% CI: 1.85-2.82) as compared to patients with no depressive symptoms. Participants with low quality of life scores and patients with high levels of symptom burden had nearly a two-fold increased odds of poor adherence (OR=1.86; 95% CI: 1.35-2.55 and OR=1.74; 95% CI: 1.07-2.84, respectively). Clinic site was not an effect modifier for any of the patient reported outcome-adherence associations. Risk category was an effect modifier of the association between hazardous alcohol use and poor adherence (test of homogeneity p-value=0.05), but did not modify any of the other patient reported outcome-adherence associations.

Conclusions: Older adults should be assessed for the risk of poor adherence. Research findings from this study may provide mental health and addiction screening tools for health care providers to assess the risk of poor medication adherence among older patients. Such screenings could identify patients who would benefit from adherence counseling or other interventions. Additional studies are needed to confirm these findings. Ultimately, better adherence would lead to improvements in viral suppression,

reductions in morbidity and mortality, and decreased risks of transmitting the virus to others.

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CHAPTER ONE: INTRODUCTION

1.1 Background

Highly active antiretroviral therapy (HAART) has dramatically changed the course of HIV infection in the U.S. HIV infection is now viewed as a chronic condition, one in which many individuals can live well into their senior years with the receipt of proper care and treatment. In the U.S., the number of individuals living with HIV aged 50 years and older has been consistently increasing. In the most recent HIV Surveillance Report, the Centers for Disease Control and Prevention (CDC) estimated that 395,668 persons over the age of 50 were living with HIV in 2013, accounting for over 42% of all persons living with HIV in the U.S. (CDC, 2014).

Drawing from the CDC epidemiological data, researchers predicted that in 2015, more than half of the individuals living with HIV in the U.S. would be over the age of 50 (Effros et al., 2008; Greene et al, 2013). There are two reasons for the increasing prevalence of HIV infection among older adults. Due to advancements in HAART, people who were diagnosed with HIV before age 50 are aging into older adulthood (Mack & Ory, 2003). Furthermore, older adults continue to become newly infected for several reasons, including the lack of condom usage because of less concern about pregnancy and the increased use of erectile dysfunction drugs (Coleman, 2003; Illa, 2008).

HAART is the combination of three or more anti-retroviral medicines used to slow the rate at which HIV multiplies. HAART cannot eliminate or destroy all of the HIV in a

person's body. The goal of HAART is to reduce the amount of HIV to an undetectable level, also known as viral suppression. Previous treatment guidelines suggested postponing the use of HAART until damage to the immune system reached particular levels. However, HAART is now recommended for all persons diagnosed with HIV infection, regardless of viral load or T-cell levels. T-cells (particularly CD4 cells) are the targeted cells for HIV, and the CD4 cell count will decrease over time due to HIV infection in the absence of HAART. HAART has been in use since 1996, and there have been numerous improvements with its development, including increased efficacy, decreased side effects, and decreased pill burden (Nachega et al, 2014). Prior treatment regimens involved taking multiple pills two or three times per day. Several regimens are available today that entail only one pill once per day.

The principal cause of treatment failure in persons living with HIV is non-adherence with HAART. Some of the factors that have been found to be associated with poor adherence include cost, limited health literacy, depression, and cognitive impairment (Gellad, Grenard, & Marcum, 2011). While several studies have suggested that older HIV-positive adults may be more adherent than younger patients (Ghidei et al, 2013; Silverberg et al., 2007; Wellons et al., 2002; Wutoh et al., 2003), few studies have focused on the issue of medication adherence for older adults living with HIV.

Given that the prevalence of older adults living with HIV is increasing, it is important to evaluate other factors that may be associated with poor medication adherence among this population. This study examined the role of several patient-reported outcomes (PROs), including alcohol and substance use, depression, quality of life, symptom burden, and physical activity level, in relation to poor HAART adherence,

using data from the Centers for AIDS Research's Network of Integrated Clinical Systems (CNICS) project. This research may help to supply guidance for providers who are treating older adults living with HIV and provide tools to assess the risk of poor medication adherence among older patients.

1.2 Significance

Data from the CDC HIV Surveillance Report indicate an increasing number of older adults living with HIV in the U.S. When comparing across age groups, the highest rate of HIV infection at the end of 2013 was among persons aged 45-49 (754.3 per 100,000), followed by those aged 50-54 (717.2 per 100,000). Those two age groups have consistently held the first and second highest rates of infection from 2011 to 2013. From 2010 to 2012, the highest percentage of individuals living with HIV was the group of persons aged 45-49. However, in 2013, the age group that had the highest percentage of people living with HIV was persons aged 50-54 (17%). Furthermore, the largest percentage increase in rates (41%) from 2010 through 2013 was among persons aged 65 and older (from 84.0 per 100,000 in 2010 to 118.5 per 100,000 in 2013) (CDC, 2014).

As the population of persons age 50 and older who are living with HIV continues to increase, more research on this population will be needed to improve medication adherence and reduce the risk of transmission. Recent research on the population of older adults living with HIV has examined factors such as risky sexual behavior (Coleman et al, 2009; Illa et al, 2010), treatment effectiveness (Althoff et al., 2010; Branas et al., 2008; Bosch, Bennett, Collier, Zackin, & Benson, 2007; Sabin et al, 2008; Silverberg et al., 2007), drug interactions and adverse effects (Marzolini et al., 2011; Sitar, 2007), and co-morbidities (Capeau, 2011; Guaraldi et al., 2011; Hasse et al., 2011).

Although some studies have examined the role of depression or substance use in medication adherence among older adults living with HIV, these studies have mostly been conducted in small numbers of patients from a single site.

The successful use of HAART can have several benefits. Viral suppression prevents or reduces the weakening of the immune system that would eventually be fatal to a person living with HIV. Furthermore, viral suppression reduces the amount of HIV in blood, semen, and vaginal fluids. This reduction in HIV levels can greatly reduce the risk of transmission to others. A study of 3,381 serodiscordant couples found that the initiation of HAART reduced the risk of HIV transmission by 92% (Donnell et al, 2010). These findings led the authors of the study to suggest that the use of HAART could be an effective means of achieving population-level reductions in HIV transmission.

Such a strategy for preventing new infections could apply to populations of all ages, including the growing number of older adults living with HIV. Older adults who are living with HIV are continuing to engage in high risk sexual behavior. In a study of 210 sexually active HIV-positive adults over the age of 45, 20% reported inconsistent condom usage and 33% reported multiple sex partners (Illa, 2008). In addition to improving health outcomes for each patient, the successful use of HAART among older adults living with HIV can also reduce the number of new infections by suppressing viral levels.

CHAPTER TWO: LITERATURE REVIEW

2.1 HIV and HAART

HIV continues to be a persistent epidemic in the U.S. The CDC estimates that over 1.2 million persons aged 13 and older are living with HIV, and that there are approximately 50,000 new infections each year (CDC, 2015). The condition now known as AIDS was first clinically observed in the U.S. in 1981 (Dolin, Mandell, & Bennett, 2010), but HIV was not discovered until 1983 (Barre-Sinoussi et al, 1983). Throughout the course of the epidemic in the U.S., white men who have sex with men (MSM) have been the demographic group with the highest HIV prevalence and incidence (Fenton, 2007). In 2010, white MSM continued to be the transmission category with the largest number of new HIV infections (n=11,200), followed closely by black MSM (n=10,600) (CDC, 2015). Since 1999, HIV incidence has continued to increase among MSM but has decreased among the risk categories of injection drug use and heterosexual contact (Buchacz, Rangel, Blacher, and Brooks, 2009).

Although white MSM continue to account for the majority of HIV cases, African Americans and Latinos are disproportionately affected. African Americans represent approximately 12% of the U.S. population, but accounted for an estimated 44% of new HIV infections in 2010. Similarly, Latinos represent approximately 16% of the U.S. population but accounted for an estimated 21% of new infections (CDC, 2015). This health disparity is seen in both the rates of new HIV infections and the rates of death among HIV-positive persons. In 2014, the rate for new HIV diagnoses per 100,000

population was 49.4 for blacks/African Americans, 18.4 for Hispanics/Latinos, and 6.1 for whites (CDC, 2015). The rates of death per 100,000 population in 2013 was 19.4 for blacks/African Americans, 4.9 for Hispanics/Latinos, and 2.5 for whites (CDC, 2015).

One of the most remarkable aspects of the epidemiology of HIV in the U.S. has been the dramatic reductions in morbidity and mortality, resulting from the widespread use of HAART (Buchacz et al, 2009). The first effective medication against HIV was zidovudine (AZT) which was approved by the U.S. Food and Drug Administration in 1987 (Molotsky, 1987). AZT is in a class of drugs named nucleoside reverse transcriptase inhibitors (NRTIs). The use of NRTIs suppressed the virus for a limited period of time, but patients still inevitably died from complications resulting from a weakened immune system (Moore & Chaisson, 1996). Eventually in 1996, a new class of drugs was used in combination with NRTIs. These drugs were in the class of protease inhibitors (PIs). A combination therapy of two NRTIs and one PI became known as Highly Active Antiretroviral Therapy (HAART) (Gulick, 1997). This treatment regimen demonstrated great success with viral suppression and resulted in a 60-80% decline in rates of AIDS, death, and hospitalization (Moore & Chaisson, 1999).

From 1992 to 1996, HIV disease was the eighth leading cause of death in the U.S. for all ages and was the leading cause of death for Americans age 25 to 44 in 1995 (CDC, 1997). The only age group in which HIV is still one of the ten leading causes of death is 25-44 years (CDC, 2015), and the death rate for that age group has been in steady decline. In 1997, the death rate for HIV disease in persons age 25-44 was 12.9 per 100,000 population. In 2007, the death rate for that age group was 5.6 per 100,000

(CDC, 2010). One of the principal reasons for this decline in death rates was the successful use of HAART (Moore & Chaisson, 1999).

The success that HAART demonstrated in reducing morbidity and mortality led to changes in treatment guidelines over time. Guidelines in the 1990s indicated that treatment should be delayed until the immune system was weakened to a particular level. This level was defined as having a CD4 cell count of less than 350 cells per cubic millimeter (Harrington & Carpenter, 2000). Current treatment guidelines in the U.S. are to initiate HAART for all HIV-infected patients, regardless of CD4 cell count or HIV viral load (Department of Health and Human Services, 2016).

2.2 HIV and Adherence

The ultimate goal of HAART is viral suppression. There are numerous benefits to suppressing the replication of HIV in the body. Viral suppression leads to reductions in the risks of morbidity and mortality (Buchacz et al, 2009). Suppressing the virus also reduces the ability of HIV to mutate and become resistant to specific treatment regimens (Penedo et al, 2003). Furthermore, viral suppression greatly reduces the risk of transmission to others. As mentioned previously, the Donnell study demonstrated that initiation of HAART led to a 92% decrease in the risk of transmission (Donnell et al, 2010). Another study demonstrated even greater success. Grinsztejn and colleagues evaluated the association between HAART and the risk of HIV transmission among 1,763 serodiscordant couples from 13 different sites across the U.S. That study found that the use of HAART reduced the risk of HIV transmission by 96% (Grinsztejn, 2014).

In order for patients to experience viral suppression and the benefits that come with viral suppression, a certain level of medication adherence must be maintained. This level

of adherence has been defined in various ways. Some scholars have defined optimal adherence as self-reporting 100% in the last two days (missing no prescribed doses) or greater than 90% over seven days (Royal et al, 2009). Others have defined optimal adherence as self-reporting 95% adherence over the past four days (Penedo et al, 2003). Some studies did not classify participants as adherent versus non-adherent. Instead, those studies have used different measures of adherence as a continuous variable. These different measures have included the use of self-reporting surveys, pill counts, or electronic data collection through the Medication Event Monitoring System (MEMS) (Liu et al, 2001). All three of these measures have demonstrated strong associations with viral load measures (Arnsten et al, 2001; Liu et al, 2001).

Few studies have evaluated the factors that are associated with adherence among the population of older adults living with HIV. However, there have been several studies that have evaluated possible associations among the general population of HIV-positive patients. Royal and colleagues evaluated self-reported data from 644 HIV-positive adults in three different states. That study found several factors that were statistically significantly associated with poor adherence. Some of those factors included greater risk of depression, younger age, not having health insurance, negative attitudes toward HIV treatment, and drug use (Royal et al, 2009). Beer and Skarbinski analyzed data on 3,606 persons living with HIV who participated in the Medical Monitoring Project (MMP) in 2009 and 2010. That study demonstrated that the following factors were associated with poor adherence: younger age, female gender, depression, stimulant use, binge alcohol use, longer time since HIV diagnosis, and patient beliefs (Beer & Skarbinski, 2014). Heckman and colleagues interviewed 329 persons living with HIV in 12 states. Based on

analysis of data from self-report surveys, that study found that the following factors were associated with consistent adherence: drinking less alcohol, having a good relationship with the physician, and engaging in more active coping in response to HIV-related life stressors (Heckman et al, 2004).

2.3 Alcohol Use, Substance Use, and Adherence

Older adults living with HIV report unhealthy levels of alcohol and substance use (Catz et al, 2001; Cohn et el, 2011; Parsons, 2013; Williams et al, 2014). Williams and colleagues examined the characteristics of alcohol use among 447 adults aged 50 years or older living with HIV (Williams et al, 2014). Participants were recruited from AIDS service organizations in nine states via posters, flyers, and direct mailings. Interested persons were asked to call a toll-free number and complete a brief telephone screening. Eligibility criteria included being 50 years or older, being HIV-positive, prescribed HAART, and reporting suboptimal adherence to HAART. Participants completed the AUDIT-C (Alcohol Use Disorders Identification Test - Consumption) survey to assess alcohol use, as well as surveys to collect data on sociodemographic characteristics and adherence. Williams and colleagues found that 15% of participants reported mild to moderate unhealthy drinking and 7% reported severe unhealthy drinking. Inclusion criteria for this study included suboptimal medication adherence, so the association between these levels of drinking and poor medication adherence could not be determined. However, the study did have participants from nine different states, and therefore, these levels of unhealthy drinking may be fairly representative of the population of older adults living with HIV.

Several studies on the general population of people living with HIV have found statistically significant associations between substance use and poor medication adherence (Malta et al, 2008). However, few studies have focused on the population of older adults living with HIV. Parsons and colleagues surveyed 557 HIV-positive adults aged 50 and older in the New York City area via telephone interview. They collected data on the number of days in the past month on which participants missed any doses of HIV medication as well as the number of days of substance use. Substance use included the use of alcohol, marijuana, cocaine/crack, opiates, amphetamines, sedatives, PCP, psychedelics, and solvents. Researchers reported that 43% of the participants who reported multiple-substance use were non-adherent. Also, members of the "multiple-substance use" class reported significantly more missed medication days on average, compared to the "no use" class ($p<0.001$) (Parsons et al, 2014). Since this study was limited to New York City residents, results may not be generalizable to other populations.

Another study examined the association between alcohol use and adherence among older adults living with HIV (Catz et al, 2001). Catz and colleagues surveyed 84 HIV-positive patients between the ages of 47 and 69 who had been prescribed HAART. The study participants were recruited through case managers at two AIDS service organizations: one in New York City and one in Milwaukee, Wisconsin. Thirty-one percent of the patients reported suboptimal adherence to HAART. Individuals who reported alcohol use within the past two months were less likely than non-drinkers to report consistent treatment adherence (OR=0.88; 95% CI: 0.79-0.98; $p=0.03$). Similarly, another study found associations between substance use and poor medication adherence among older adults living with HIV (Cohn et al, 2011). Although not restricted to

patients aged 50 years and older, Cohn and colleagues followed 433 individuals living with HIV for 10 years. At baseline, 50% of study participants were aged 40 years or older. Participants in the study were recruited from the AIDS Clinical Trials Group (ACTG) 362, which was a prospective, multi-center study in the U.S. At the conclusion of the 10 year follow-up period, people who reported cocaine, amphetamine, or heroin use in the past 30 days had over twice the odds of poor medication adherence as compared to non-users (OR=2.14; 95% CI:1.36-3.38; p=0.001).

2.4 Depression and Adherence

Similar to the research findings regarding substance use and adherence, there have been numerous studies that have found associations between depression and poor medication adherence among individuals living with HIV (Rao et al, 2007; Reynolds et al, 2004; Voss et al, 2007; Wagner et al 2011, Willig et al, 2008). Most of these studies did not focus on the population of older adults, but examined these associations among the population of all adults living with HIV. At least one study found an association between increasing age and depression among people living with HIV (Justice et al, 2004). Justice and colleagues examined data from the Veterans Aging Cohort Five-Site Study (VACS 5). The VACS 5 enrolled 1,803 patients from Veterans Affairs clinics in Georgia, New York, Texas, and California. Study participants ranged in age from 30 to 85 years, and 1,047 of them were living with HIV. Each participant completed the PHQ-9 (Patient Health Questionnaire) to measure levels of depressive symptoms. Justice and colleagues compared the prevalence of lifetime depression among five age categories: (1) 30-39 years, (2) 40-49 years, (3) 50-59 years, (4) 60-69 years, and (5) $\geq$70 years. Researchers found that the interaction between HIV and increasing age was significant.

Increasing age was associated with an increased risk of depression among HIV-positive participants when compared with HIV-negative participants (OR=1.33; 95% CI: 1.04-1.71; p=0.02).

Two studies that evaluated the association between poor medication adherence and depression among older adults living with HIV are the Frain and Bianco studies. Frain and colleagues recruited 130 patients from an infectious disease clinic at a Midwestern university medical center (Frain et al, 2014). Study participants were equally divided into two groups by age: (1) 18 to 49 years and (2) 50 years and older. Each participant completed both the Center for Epidemiological Studies Depression Scale (CES-D) and the Medication Management Task - Revised (MMT-R). Analyses from that study demonstrated that depressive symptoms among older adults living with HIV were predictors of poor medication management. Depressive symptoms accounted for 6% of the unique variance in medication management scores ($p<0.05$). This study was limited by the relatively small number of participants, as well as by using a single infectious disease clinic as a recruitment site.

The Bianco study focused on gender differences in patterns of adherence among older adults living with HIV (Bianco et al, 2011). Bianco and colleagues conducted telephone interviews with 242 HIV-infected persons age 50 years or older. Participants were recruited through AIDS service organizations in 25 different states. A total of 162 participants were male with a median age of 57.74 years, and 80 were female with a median age of 57.05 years. Among other assessment instruments, researchers utilized the Geriatric Depression Scale and the AIDS Clinical Trials Group Adherence Questionnaire (ACTG). Results indicated that moderate to severe depression predicted poor medication

adherence among older adult men living with HIV (p=0.034). However, the presence of depressive symptoms was not associated with poor adherence among older women (p=0.489).

2.5 Quality of Life and Adherence

Few studies have examined the association between quality of life and medication adherence among individuals living with HIV. Some studies have demonstrated that people living with HIV have lower average quality of life scores. O'Cleirigh and Safren recruited 152 individuals living with HIV at a single community health center. Study participants completed the Quality of Life Inventory (QOLI), resulting in an average QOLI score of 1.23. This average score placed the participants below the 20th percentile of the normative sample for this instrument and in the classification range of "low life satisfaction" (O'Cleirigh & Safren, 2006). Miners and colleagues enrolled 154 individuals living with HIV in a study to compare health-related quality of life among this population to the general population. Study participants completed the European Quality of Life (EQ-5D) questionnaire, and scores were compared to those of the general population. After adjusting for differences in age and gender, the individuals living with HIV reported statistically significant lower scores (p=0.0001) (Miners et al, 2001).

These low quality of life scores among the population of people living with HIV have prompted some researchers to examine the associations between quality of life and other factors, such as medication adherence or the initiation of HAART. One study found that improvements in adherence were associated with increased scores on quality of life measures. Mannheimer and colleagues collected quality of life and medication adherence data from 514 participants from 15 sites throughout the U.S. The study

included adults of all ages, with the mean age being 39 years. Study participants completed the Short Form 12 (SF-12) and reported levels of adherence every 4 months for 12 months. Participants were classified as adherent if they reported 100% adherence at 3 or 4 of the 4 follow-up study visits. The SF-12 has two summary scores: the physical component summary (PCS) score and the mental component summary (MCS) score. At 12 months, adherent participants had a higher mean PCS score (49.20 vs. 46.15, $p<0.001$) and a higher mean MCS score (45.87 vs. 42.93, $p<0.001$), compared to scores in the non-adherent group. Participants reporting 100% adherence achieved higher quality of life scores at 12 months, compared to those with poorer adherence. Patients reporting at least 80% adherence demonstrated smaller gains in quality of life scores, and patients reporting less than 80% adherence demonstrated reductions in quality of life scores (Mannheimer et al, 2005).

Similar results were found in a study of older adults living with HIV. Brent analyzed data from 914 adults over the age of 50 living with HIV in New York City. The average age of participants was 55.5 years. Participants completed the modified Medical Outcomes Survey (MOS) short form, providing an average quality of life score based on five scales related to physical function, cognitive function, social function, pain, and energy/fatigue. Although adherence levels were not measured, the population of individuals receiving HAART was compared to those not receiving treatment. The population of older adults receiving HAART demonstrated higher scores on the quality of life measure ($p=0.021$) (Brent, 2012).

When evaluating associations between quality of life and medication adherence, most studies have looked at quality of life as an outcome variable. At least one study

examined this association among persons living with HIV, using medication adherence as the outcome variable. However, the study was not restricted to the population of older adults living with HIV. Penedo and colleagues collected data on 116 HIV-positive adults, with a mean age of 39.2 years. Study participants completed the HIV/AIDS-Targeted Quality of Life (HAT-QoL) instrument and the Adherence to Combination Therapy Guide (ACTG). Higher scores on the HAT-QoL indicated a statistically significant association with better medication adherence ($p<0.01$) (Penedo et al, 2003).

2.6 Symptom Burden and Adherence

A few studies have examined the association between symptom burden and medication adherence among individuals living with HIV. However, none of these studies have focused on the population of older adults. Corless and colleagues conducted a cross-sectional study of 50 individuals living with HIV. Study participants were recruited from a community-based clinic in a major metropolitan area in the northeastern U.S. Self-reported data were collected from participants on the number and severity of symptoms, quality of life, and medication adherence. Statistically significant associations were found between measures of symptom burden and adherence. Individuals who reported being "bothered by symptoms" were more likely to forget to take medications ($p=0.003$), have difficulty taking medications ($p=0.04$), or discontinue medications when feeling better ($p=0.007$). Intensity of symptoms was also associated with discontinuing medications when feeling better ($p=0.047$) (Corless et al, 2005).

Similar results were found in a larger study by Gonzalez and colleagues, who collected data on 325 individuals living with HIV. Study participants ranged in age from 18 to 65, with a median age of 40.9 years. Participants were enrolled in a 15-month

longitudinal study and were interviewed at baseline, at three months, and then at six month intervals for one year. Participants were surveyed about the presence of various symptoms and also completed the Adherence to Combination Therapy Guide (ACTG). Results from this study demonstrated a statistically significant association between symptoms and adherence, with a greater number of symptoms associated with poorer medication adherence ($p<0.05$) (Gonzalez et al, 2007).

2.7 Physical Activity Level and Adherence

Although there have been some studies on physical activity among the population of persons living with HIV, most of these studies have focused on the possible benefits of increased physical activity, such as decreases in depressive symptoms or decreases in viral load (Bopp et al, 2004). A review of the literature provides one study that has evaluated the relationship between physical activity and HAART adherence. However, the study was not restricted to the population of older adults and was restricted to the population of MSM. Blashill and colleagues analyzed data on 860 HIV-positive MSM from four clinic sites in four different states (California, Washington, Alabama, and Massachusetts). Researchers used data collected during the CNICS project, the same data set that was used in this study. Using patient reported outcomes data on medication adherence and physical activity levels, Blashill and colleagues found a statistically significant association between the two variables. Individuals who reported lower levels of physical activity were at higher risk of non-adherence ($p=0.009$). Further analysis led the researchers to suggest that increases in physical activity levels may reduce the presence of depressive symptoms, which then may improve medication adherence (Blashill et al, 2013).

2.8 Summary and Conclusions

Major limitations of these previous studies include the small number of participants (Catz et al, 2001; Corliss et al, 2005) and the inability to generalize to other populations due to the fact that the studies considered special populations (e.g. veterans; men who have sex with men) (Blashill et al, 2013; Justice et al, 2004) or were in limited geographic areas (Brent, 2012; Catz et al, 2001; Frain et al, 2014; Gonzalez et al, 2007; Parsons et al, 2014). Compared to these prior studies, this study had a larger sample size and had representation from several different regions of the U.S. A total of 3,309 study participants met the eligibility criteria for this study, with 817 of those participants meeting the criteria for being classified as non-adherent. Furthermore, this study focused on the population of older adults living with HIV, which has not been considered in previous studies on the association between many of these factors and medication adherence. As the population of older adults becomes the majority of individuals living with HIV, understanding how alcohol and substance use, depression, quality of life, symptom burden, and physical activity affect HAART adherence has important public health implications. By modifying these factors and increasing HAART adherence, individuals living with HIV may have a lower risk of morbidity and mortality, as well as a decreased risk of transmitting the virus to others.

2.9 Research Hypotheses

H1: Individuals who are classified as hazardous drinkers will have increased odds of poor adherence to a HAART regimen.

H2: Individuals with current or past substance use will have increased odds of poor adherence to a HAART regimen.

H3: Individuals with depressive symptoms will have increased odds of poor adherence to a HAART regimen.

H4: Individuals with lower scores on the Quality of Life survey will have increased odds of poor adherence to a HAART regimen.

H5: Individuals who report higher levels of symptom burden will have increased odds of poor adherence to a HAART regimen.

H6: Individuals who are more physically active will have decreased odds of poor adherence to a HAART regimen.

H7: The patient reported outcomes (PRO)–adherence association will differ by clinic site.

H8: The patient reported outcomes (PRO)–adherence association will differ by risk category.

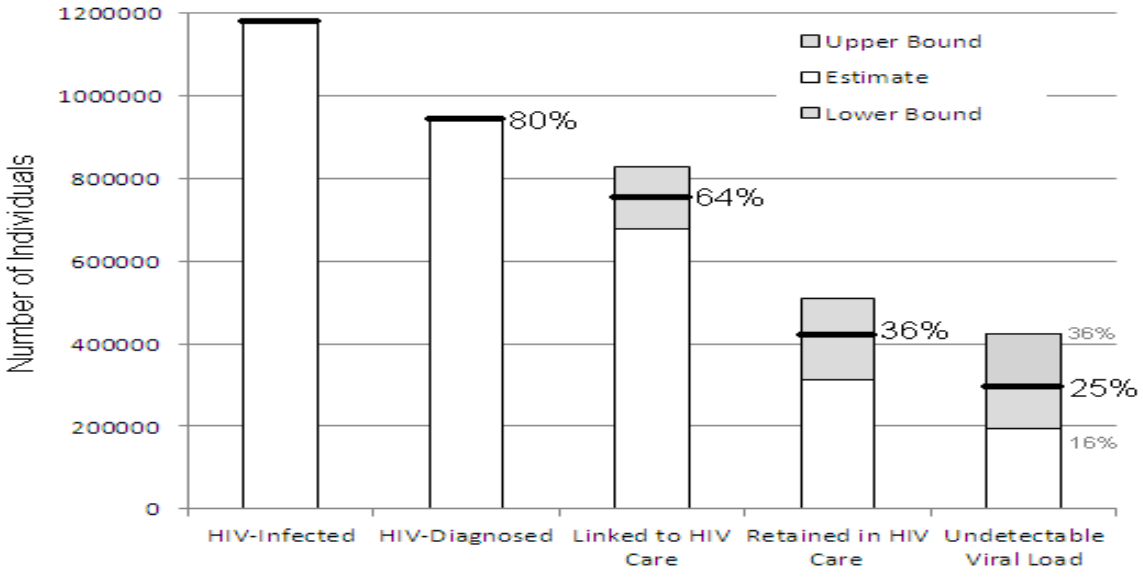
H9: The relationship between depression and adherence will be mediated by current substance use.

H10: The relationship between depression and adherence will be mediated by hazardous alcohol use.

CHAPTER THREE: METHODS

3.1 Conceptual Frameworks

This study is based on concepts from Gardner's Cascade of Care Model and Andersen's Behavioral Model of Health Services Use. Gardner and colleagues published a new model of engagement in care for HIV-infected individuals in 2011 (Gardner et al, 2011). This model expanded the spectrum of engagement in HIV care to include a minimum of five categories. These categories are (1) HIV-infected, (2) HIV-diagnosed, (3) linked to HIV care, (4) retained in HIV care, and (5) viral suppression (Figure 1).



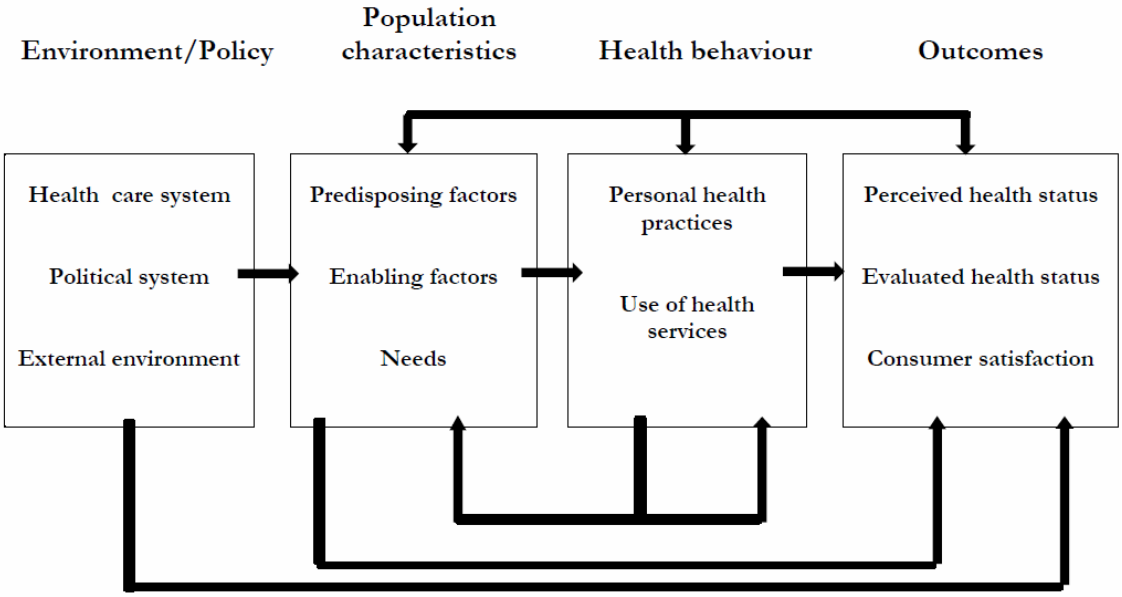
Adapted from Gardner, et al. Clin. Infect. Dis. 2011;52(6):793-800.
Figure 1: Cascade of care for individuals living with HIV in the United States

At the time the model was developed, only 25% of individuals living with HIV in the U.S. were in the category of viral suppression, meaning that the patient is retained in HIV care, adhering to a HAART regimen, and has an undetectable viral load. In order to reduce the number of new infections, the number of individuals in this fifth category must increase dramatically. This study focused on the last two categories: retained in HIV care and virally suppressed. Participants in the CNICS study are already retained in HIV care. This study sought to determine what factors may be significantly associated with poor medication adherence, which would prevent those patients from being classified in the fifth category, viral suppression. The factors that were explored included alcohol and substance use, depression, quality of life, symptom burden, and physical activity level.

Several theoretical frameworks were considered to demonstrate how these factors may be associated with the desired health outcome of optimal adherence to HAART, including the Chronic Care Model, the Precede-Proceed Model, the Health Belief Model, and the Andersen Behavioral Model of Health Services Use. Various components of these models, however, were missing from the available data set. For example, the Chronic Care Model and the Health Belief Model would require some measure of an individual's self-efficacy regarding the perceived ability to successfully adhere to the medication regimen. However, such a measure is not collected in the CNICS project. The Precede-Proceed Model would be ideal for a longitudinal study on the planning, implementation, and evaluation stages of an intervention, such as the decision to begin HAART. However, essential components of the model, such as the knowledge, attitudes,

and beliefs of individuals before the initiation of HAART, are not collected in the CNICS project.

The model that best demonstrates how alcohol and substance use, depression, quality of life, symptom burden, and physical activity level play a role in medication adherence is the Andersen Behavioral Model of Health Services Use (Figure 2) (Anderson, 1995).



Adapted from R.M. Andersen. Revisiting the behavioral model and access to medical care: does it matter? J. Health Social Behavior 1995; 36: 1-10
Figure 2: The Anderson behavioral model of health services use

The Anderson Behavioral Model of Health Services Use is a conceptual framework that has been used to describe various factors that may be associated with health care use (Anderson & Davidson, 2007). The model examines both contextual and individual characteristics, and illustrates their dynamic relationship to health behaviors and health

outcomes. This study included elements of population characteristics, health behaviors, and health outcomes.

3.1.1 Environmental Characteristics

The characteristics of the environment are measured on the aggregate level, such as a particular population or geographical region. These characteristics are categorized into predisposing, enabling, and need characteristics. Predisposing characteristics include the demographics of the community, such as age, gender, ethnicity, and marital status. Also included in this category are social characteristics, such as educational levels, employment levels, or crime rates. Belief characteristics in the predisposing category include underlying community or organizational values and cultural norms.

Enabling characteristics include the following sub-categories: health policy, financing, and organization. Health policy includes public policies that are established by the government, as well as private policies, such as those formulated by managed care organizations. Financing characteristics include aggregate measures such as per capita income, rates of insurance coverage, and per capital expenditures for health services. Organization characteristics include the amount of health care services within the community and the structure of those services. These characteristics may include the ratios of providers to population, the mix of provider specialties, and provider locations and hours of operation.

Need characteristics include the sub-categories of environmental need and population health indices. Environmental needs are health-related measures of the physical environment, such as air and water quality or homicide rates. Population health

indices include such measures as infant mortality rates, morbidity rates, and disability rates.

3.1.2 Individual / Population Characteristics

Individual characteristics have the same three categories as environmental characteristics, although these characteristics are measured on the individual level. Demographic factors under the individual predisposing characteristics are similar to those of the contextual characteristics, such as age, race/ethnicity, and gender. Other predisposing factors include social factors, such as occupation and level of education, and health beliefs, such as individual values, attitudes, and knowledge about health and health services. This study examined three predisposing factors: hazardous alcohol use, substance use, and depression.

Enabling characteristics for individuals include both financing and organization factors. Financing factors consist of income, wealth, and the price of health care to the individual. Organization factors may include the presence of a regular source of health care, means of transportation, and travel time to a health care provider.

Individual need characteristics can be categorized as perceived or evaluated need. Perceived need includes the individual's view of personal health status and the magnitude of a health problem. Evaluated need can include a provider's judgment or an objective measurement of health status and the need for medical care. In this study, symptom burden is an individual need characteristic.

3.1.3 Health Behaviors and Health Outcomes

Each of the environmental and individual characteristics influences the health behaviors and health outcomes of individuals. Health behaviors include personal health

practices, such as diet, exercise, and adherence to medical regimens. Other health behaviors include the process of medical care (i.e. the behavior of health care providers) and the use of personal health services, such as hospital or dental care visits. Health outcomes include perceived health status, evaluated health status, and consumer satisfaction. In this study, quality of life and medication adherence are both health outcomes, and physical activity level is a health behavior.

The Andersen model suggests that health services use is a function of the predisposition to use such services, various factors that enable or limit use, and a person's need for care. The model also illustrates the dynamic positions of these elements, recognizing that health behaviors and health outcomes also influence the individual characteristics, as well as other health behaviors and outcomes.

3.1.4 Summary and Conclusions

This study uses the Andersen Behavioral Model to examine associations between various factors and HAART adherence in the population of older adults. The goal of the study was to determine if any of these factors can be used to assess for the risk of poor medication adherence. If patients are then able to be classified as high risk for poor adherence, these patients would be priority candidates for adherence counseling or similar services, in order to increase the percentage of patients in the category of viral suppression on the Cascade of Care model.

3.2 Study Design and Population

This cross-sectional study is a secondary data analysis of data from the Centers for AIDS Research's (CFAR) Network of Integrated Clinical Systems (CNICS) research study. There are currently 18 CFAR sites in the U.S. Eight of those CFAR sites are

CNICS partners. This study analyzed data collected from seven CNICS study sites between 2010 and 2014. These sites include the University of Alabama-Birmingham, the University of Washington, The University of California-San Diego, the University of California-San Francisco, Fenway Community Health Center of Harvard University, Johns Hopkins University, and the University of North Carolina-Chapel Hill. The excluded site (Case Western Reserve University) does not collect data on patient reported outcomes (PROs).

CNICS was funded in 2006 by the National Institutes of Health to provide an infrastructure of data that can be used for conducting research on HIV clinical outcomes. Individuals are continuing to be recruited. As of 2015, a total of 31,824 patients had been enrolled in the project. Data are collected in a convenience sample of HIV-positive individuals who receive medical care at the CNICS sites. Participants are approached by their physician in a private location (generally the patient's private exam room in the medical clinic) and informed about the study. Informed consent procedures are then followed with those individuals who express an interest in participating in the study. Inclusion criteria for participation in the CNICS study include the following: current patient at one of the CNICS sites; HIV positive; 18 years of age or older; able and willing to provide informed consent for the completion of questionnaires and the collection of blood specimens; and able to answer questions using a simple computer screen questionnaire.

The CNICS project maintains the following types of data: (1) disease diagnoses, (2) laboratory data, (3) medication data, (4) demographics, (5) health care utilization, (6) vital status, (7) patient reported outcomes, (8) antiretroviral drug resistance,

(9) biological specimens, and (10) census block data. Patient Reported Outcomes (PRO) survey data are collected at CNICS sites during routine clinical encounters, using touch-screen tablets or PCs connected to a wireless network, protected by encryption software. Researchers are available to lend assistance with completing the surveys. Patients complete a clinical assessment every 4 to 6 months that includes the following domains: depression and anxiety; HAART adherence; smoking, alcohol, and drug use; sexual risk behaviors; symptom burden; physical activity level; and quality of life.

All data used for analysis were obtained from the CNICS composite medical database system and quality assured via the CNICS Research Platform. Data were requested from CNICS on all patients who completed the PRO surveys and had filled a prescription of HAART at least one time during the previous four years. There were a total of 7,463 individuals in the data set obtained from CNICS. Eligibility criteria for this study were that participants had to be age 50 or older at the time that the most recent PRO survey was completed. A total of 4,127 participants were excluded because they were under age 50. There were 27 transgender patients in the data set. Although birth sex for these patients was included in the data set, the date of sex change was not available and may have occurred during the time frame of the study. Therefore, this small number of patients was excluded from the study. Thus, a total of 3,309 study participants met the eligibility criteria, with 817 of those participants classified as non-adherent to their HAART regimen.

3.3 Exposure Variables

Exposure variables for this study included current hazardous alcohol use, substance use, depression, quality of life, symptom burden, and physical activity level.

The Alcohol Use Disorders Identification Test (AUDIT-C) is a three-question, self-report screening test that is used to identify individuals who are hazardous drinkers. These questions are: (1) How often do you have a drink containing alcohol?, (2) How many standard drinks containing alcohol do you have on a typical day?, and (3) How often do you have six or more drinks on one occasion? Answers to these questions are then used to provide a score between 0 and 12. A score of 4 or above for men and 3 or above for women has been established as a valid threshold for classifying an individual as "at-risk" for being a hazardous drinker (Bradley et al, 2003; Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). This survey tool enabled the use of a dichotomous variable, where the exposed are hazardous drinkers and the unexposed are non-hazardous drinkers or non-drinkers.

The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) was developed by the World Health Organization to detect and manage substance use in health care settings. The self-reporting tool has been assessed by multiple researchers as a valid and reliable survey instrument (Newcombe, Humeniuk, & Ali, 2005; WHO ASSIST Working Group, 2002). Scores from the ASSIST survey instrument allowed study participants to be classified into one of three categories: (1) no substance use, (2) past use, or (3) current substance use. Substance use was defined as using any cocaine, opiates, or amphetamines. Current substance use was defined as using any of these three substances within the past three months.

The Patient Health Questionnaire (PHQ-9) is a multiple-choice, self-report survey that has been used in multiple studies and clinical settings to assess for depressive symptoms. Scores from the PHQ-9 were used to classify each study participant into one

of four categories of depression severity. These categories are: (1) none, (2) mild depression, (3) moderate depression, or (4) severe depression. The PHQ-9 has repeatedly been assessed as an efficient and valid measure of the presence of depressive symptoms (Spitzer, Kroenke, & Williams, 1999).

The EuroQol (EQ-5D) questionnaire is a five-question, self-reporting survey that measures health-related quality of life. Response options for each dimension are (1) no problems, (2) moderate problems, or (3) extreme problems. Scores from this survey tool were used to classify each participant into one of three categories of health-related quality of life: (1) low, (2) medium, or (3) high. This survey tool has also been assessed as a reliable and valid measure of health-related quality of life (Shaw, Johnson, & Coons, 2005).

The HIV Symptom Index is a self-reporting survey that lists 20 different HIV-related symptoms and asks the participant to select a score of 0 to 4 for each one (0 = "I do not have this symptom; 1 = "I have this symptom and it does not bother me"; 2 = "I have this symptom and it bothers me a little"; 3 = "I have this symptom and it bothers me"; or 4 = "I have this symptom and it bothers me a lot"). Scores from this survey were used to classify study participants into one of three categories of symptom burden: (1) low, (2) medium, or (3) high. This survey tool has also been assessed and determined to demonstrate high levels of construct validity (Justice et al, 2001).

The Lipid Research Clinics Physical Activity Questionnaire (LRCPAQ) is a four-question, self-reporting survey that has been used in multiple research studies to assess the physical activity levels of study participants. The first two questions concern work and leisure activities, with the participants asked to compare their activity level to others

of their age and sex on a qualitative scale. The third question asks if the participant engages in strenuous exercise or hard physical labor. The last question assesses frequency asking, "Do you exercise or labor at least three times per week?" The scores from this survey were used to classify a participant into one of four categories. Those categories are: (1) not physically active, (2) low level of physical activity, (3) moderate level of physical activity, or (4) high level of physical activity. The survey tool has repeatedly been assessed as both reliable and valid (Ainsworth, Jacobs, & Leon, 1993).

3.4 Outcome Variable

The outcome variable (adherence) was dichotomized, based on the research findings of Feldman and colleagues when also analyzing data from the CNICS project (Feldman et al, 2013). Feldman's study found that two self-reported responses to the AIDS Clinical Trial Group (ACTG) Adherence Instrument were significantly associated with a detectable viral load, meaning that the patient is not experiencing viral suppression. As mentioned previously, the principal cause of treatment failure is non-adherence. These two responses were to the question about the last missed dose of medication and were (1) "within the past week" and (2) "1-2 weeks ago." These two responses were classified as non-adherent, with all other responses classified as adherent. The other responses include: (1) "2-4 weeks ago", (2) "1-3 months ago", (3) "more than 3 months ago", and (4) "never skip medications or not applicable."

3.5 Potential Confounding Variables

The study controlled for demographic factors such as race/ethnicity, gender, and age. For race/ethnicity, participants were classified as non-Hispanic white, non-Hispanic black, Hispanic, or other. Participants were classified by birth sex as male or female.

Age categories were (1) 50-54 years, (2) 55-59 years, (3) 60-64 years, or (4) greater than age 64. Another potential confounding variable is clinic site, since different locations and different methods of data collection may have unpredictable effects on associations. As mentioned previously, there were seven clinics from various regions of the U.S. that provided patient data for this study: the University of Alabama-Birmingham, the University of Washington, the University of California-San Diego, the University of California-San Francisco, Fenway Community Health Center of Harvard University, Johns Hopkins University, and the University of North Carolina-Chapel Hill. Other possible confounders included the risk factor for acquiring HIV. The CNICS project already classified study participants into one of the possible CDC-defined risk categories. These included the following categories: (1) injection drug user, (2) male who has sex with other males, (3) heterosexual contact, and (4) other risk factor (hemophilia, receipt of blood transfusion, or occupational exposure). Another possible confounder is co-morbidity with another chronic illness. The use of medications for the treatment of cardiovascular disease and/or diabetes enabled the use of a dichotomous variable for the presence of at least one other chronic illness.

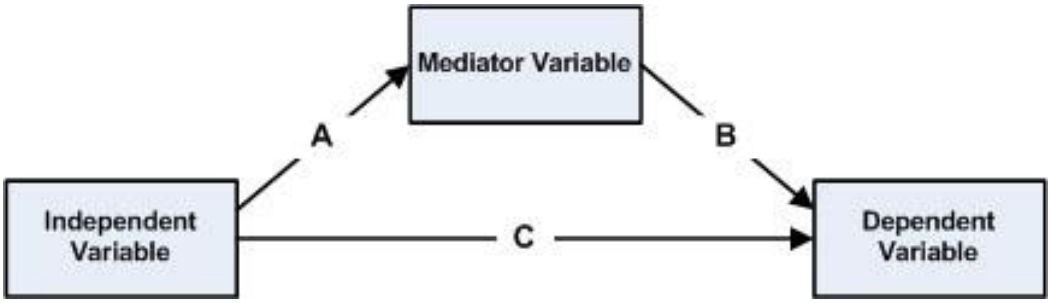
3.6 Statistical Analyses

Descriptive statistics were calculated for the entire sample and the sample of the study population that was classified as non-adherent. Comparisons of categorical variables were made using chi-square tests. P-values <0.05 were considered statistically significant. Unadjusted logistic regression analyses were conducted to explore relationships between the patient reported outcomes (PROs) and HAART medication adherence by estimating odds ratios (OR) and 95% confidence intervals (CI).

Multivariate logistic regression models were then created for each of the PRO–adherence associations, adjusting for the following variables: age category, race/ethnicity, gender, clinic site, co-morbidity with another chronic illness, and risk factor. In addition, backward elimination was used to create reduced models that contained only those variables that were significant at the 0.10 level.

To assess whether clinic site was an effect modifier of the association between each of the PROs and medication adherence, a stratified analysis was conducted. Similarly, a stratified analysis was used to evaluate whether risk factor was an effect modifier of any of the PROs-adherence associations. Furthermore, mediation analyses were conducted to explore whether depression affects substance use or hazardous alcohol use, resulting in poor medication adherence (figure 3). The mediation analysis consisted of the traditional four steps for testing mediation (Baron & Kenny, 1986).

For the first mediation analysis, the requirements for testing mediation were: (1) depression should predict medication adherence; (2) depression should predict substance use; (3) substance use should be significantly associated with medication adherence; and (4) the effect of depression on medication adherence should be attenuated when substance use is statistically controlled. For the second mediation analysis, the requirements for testing mediation were (1) depression should predict medication adherence; (2) depression should predict hazardous alcohol use; (3) hazardous alcohol use should be significantly associated with medication adherence; and (4) the effect of depression on medication adherence should be attenuated when hazardous alcohol use is statistically controlled. All data analyses were performed using SAS version 9.4 (SAS Institute, 2015).



From Baron & Kenny. J. Pers. Soc. Psychol. 1986; 51, 1173-1182.
Figure 3: Mediation model

For comparison purposes, analyses of the associations between patient reported outcomes and adherence were conducted on the population of younger adults (age 18-49 years) in the CNICS data set. Descriptive statistics were calculated, and comparisons of categorical variables were made using chi-square tests for the younger population. P-values <0.05 were considered statistically significant. Multivariate logistic regression models were then used to provide estimates of multivariable odds ratios and corresponding 95% confidence intervals. Backward elimination was used to create reduced models that contained only those variables that were significant at the 0.10 level.

CHAPTER FOUR: RESULTS

4.1 Participant Characteristics

The majority of the study population was male (85%) and non-Hispanic White (54%) (table 1). Approximately 75% of the population were adherent, and 25% were non-adherent. Differences between the two groups were not statistically significant for gender or race ($p=0.350$ and $p=0.597$, respectively). Among participants classified as adherent, most were male (85%) and non-Hispanic White (55%). In comparison, among the non-adherent participants, 84% were male and 54% were non-Hispanic White.

The majority of the study population were in the youngest age category of 50-54 years (46%). However, there were statistically significant differences in age between the two adherence groups ($p<0.0001$). Among the adherent participants, 44% were in the youngest age category of 50-54 years, and 10% were in the oldest age category of 65-86 years. In comparison, among the non-adherent group, 53% were age 50-54 years and only 6% were in the oldest age category of 65-86 years.

The majority of study participants received care from the clinics at the University of California-San Diego (30%) and the University of Alabama-Birmingham (22%). The clinic with the smallest number of participants was the University of North Carolina-Chapel Hill (7%). There were statistically significant differences in clinic sites between the adherent and non-adherent participants ($p<0.0001$). The largest differences among clinic sites were the clinics at the University of Washington and the University of California-San Francisco. Among the non-adherent population, 15% were from the

University of Washington clinic, and 14% were from the University of California-San Francisco. In comparison, among the non-adherent group, 11% were from the University of Washington clinic, and only 8% were from the University of California-San Francisco.

Among risk categories, the total study population had 56% of participants classified as men who have sex with other men, followed by heterosexual contact (34%) and injection drug use (5%). There were statistically significant differences between the adherent and non-adherent groups by risk category ($p=0.04$). While the percentage of men who have sex with other men was identical in the two groups (56%), there were slight differences with respect to heterosexual contact (adherent: 34%, non-adherent: 36%) and injection drug use (adherent: 6%, non-adherent: 3%).

There was also a significant difference between the adherent and non-adherent groups for the comorbidity of another chronic illness ($p=0.01$). For the total study population, 56% of participants had another chronic illness. Among the adherent participants, 57% had another chronic illness whereas among the non-adherent group, only 52% had another chronic illness.

Frequencies were statistically significantly different among all of the patient reported outcomes (PROs), with the one exception of physical activity level ($p=0.06$). More of the non-adherent group were classified as hazardous alcohol drinkers (25% compared to 18% in the adherent population; $p<0.0001$). Similarly, more of the non-adherent group were classified as current substance users (21% compared to 7% in the adherent population; $p<0.0001$). However, among past substance users, the frequency was slightly lower among the non-adherent group (33% compared to 35% in the adherent population). More of the non-adherent group reported depressive symptoms in all three categories of

depression (mild, moderate, and severe; $p<0.0001$). Also, more of the non-adherent group reported lower health-related quality of life scores ($p<0.0001$) and higher levels of symptom burden ($p<0.0001$). The non-adherent group was less physically active than the adherent population, but this difference was not statistically significant ($p=0.06$).

4.2 Unadjusted Associations Between Select Characteristics and Adherence

There were no statistically significant associations between gender or race/ethnicity and poor medication adherence (OR=1.11; 95% CI: 0.89-1.38 and OR= 1.01; 95% CI: 0.90-1.13, respectively) (table 2). There was a statistically significant dose-response relationship between age and poor medication adherence. As age increased, the odds of poor adherence decreased (age 55-59: OR=0.75; 95% CI: 0.63-0.91; age 60-64: OR=0.69: 95% CI: 0.55-0.88; and age 65-86: OR=0.51; 95% CI: 0.37-0.70 vs. referent of age 50-54). Among the categories of risk factors, only one factor was significantly associated with poor adherence. Specifically, injection drug users had 48% lower odds of poor adherence (OR=0.52; 95% CI: 0.34-0.81), when compared to the participants in the risk category of heterosexual contact.

There were two clinics with statistically significant associations with poor adherence. Individuals at the San Francisco clinic had nearly twice the odds of being non-adherent, in comparison to individuals at the San Diego clinic (OR=1.81; 95% CI: 1.38-2.38). Individuals at the University of Washington clinic had 1.43 times the odds of being non-adherent when compared to individuals at the San Diego clinic (OR=1.43; 95% CI: 1.10-1.85). Patients at the other four clinics had decreased odds of being non-adherent, but the associations were not statistically significant.

There were statistically significant associations between all of the patient reported outcomes and adherence, with the one exception of physical activity level. There was a dose-response relationship between physical activity level and adherence. As physical activity levels increased, the odds of poor adherence decreased. When compared to patients who were not physically active, patients who reported low, moderate, or high levels of physical activity had decreased odds of poor adherence (OR=0.91; 95% CI: 0.74-1.10, OR=0.82; 95% CI: 0.62-1.07, and OR=0.80; 95% CI: 0.61-1.06, respectively).

Individuals who were classified as hazardous alcohol drinkers had 1.55 times the odds of being non-adherent (OR=1.55; 95% CI: 1.28-1.87). Similarly, individuals with substance use had increased odds of poor adherence. Individuals who reported past substance use had 30% increased odds of being non-adherent, in comparison with individuals who reported no past substance use (OR=1.30; 95% CI: 1.07-1.58), and individuals who reported current substance use had almost 4 times the odds of being non-adherent (OR=3.98; 95% CI: 3.09-5.14).

Individuals who reported depressive symptoms also had higher odds of being non-adherent. Participants who were classified as having mild depressive symptoms had 1.58 times the odds of poor adherence (OR=1.58; 95% CI: 1.30-1.92). Individuals with moderate depressive symptoms had twice the odds of being non-adherent (OR=2.31; 95% CI: 1.88-2.84), and individuals with severe depressive symptoms had 1.67 times the odds of being non-adherent (OR=1.67; 95% CI: 1.13-2.48).

There was a statistically significant dose-response relationship between scores on the quality of life scale and poor medication adherence. As quality of life scores decreased, the odds of poor adherence increased. Individuals with medium scores on the quality of

life scale had 1.46 times the odds of being non-adherent (OR=1.46; 95% CI: 1.21-1.77), in comparison to those individuals with high scores on the quality of life scale. Individuals with low scores on the quality of life scale had even greater odds of being non-adherent (OR=1.88; 95% CI: 1.37-2.57).

There was also a dose-response relationship between symptom burden and poor adherence. As symptom burden levels increased, the odds of poor adherence also increased. Individuals who were classified as having medium levels of symptom burden had 43% increased odds of poor adherence (OR=1.43; 95% CI: 1.16-1.76), when compared to those individuals with low levels of symptom burden. Individuals who were classified as having high levels of symptom burden had almost twice the odds of being non-adherent (OR=1.90; 95% CI: 1.17-3.09), in comparison to individuals with low levels of symptom burden.

4.3 Adjusted Associations Between Patient Reported Outcomes and Adherence

When adjusted for age, chronic illness co-morbidity, clinic site, risk category, race/ethnicity, and gender, the association between alcohol use and poor adherence remained relatively unchanged for hazardous drinkers as compared with non-hazardous drinkers (OR=1.51; 95% CI: 1.25-1.83; table 3). The magnitude of the OR in the reduced model, adjusted for age, chronic illness comorbidity, clinic site, and risk category, was also similar to the unadjusted and full models and retained statistical significance (OR=1.50; 95% CI: 1.24-1.82).

The full model for the substance use-adherence association remained statistically significant; however, the magnitudes of the associations were attenuated. Specifically, current users had 3.82 times the odds and past users had 1.27 times the odds of poor

adherence as compared to participants who reported no substance use (OR=3.82; 95% CI: 2.94-4.95 and OR=1.27; 95% CI: 1.04-1.55, respectively). Findings from the reduced model, adjusted for age, gender, and clinic site were similar to the findings in the full model (OR=3.83; 95% CI: 2.96-4.94 and OR=1.26; 95% CI: 1.04-1.54, respectively).

The full model for the association between depressive symptoms and adherence also remained statistically significant, and the magnitudes of those associations decreased for individuals with moderate or severe depressive symptoms when compared to individuals with no depressive symptoms (OR=2.28; 95% CI: 1.85-2.82 and OR=1.56; 95% CI: 1.05-2.32, respectively). For individuals with mild depressive symptoms, there was no change in magnitude from the unadjusted model (OR=1.58; 95% CI: 1.30-1.93). The reduced model was adjusted for age, chronic illness comorbidity, clinic site, and risk category, and the findings were similar to the full model (mild: OR=1.57; 95% CI: 1.29-1.92, moderate: OR=2.26; 95% CI: 1.83-2.79, and severe: OR=1.55; 95% CI: 1.04-2.31).

The association between health-related quality of life and adherence remained statistically significant and changed very little in the full model for individuals with medium or low level scores, compared to those individuals with high scores (OR=1.47; 95% CI: 1.21-1.79 and OR=1.86; 95% CI: 1.35-2.55, respectively.) The magnitude of the ORs in the reduced model, adjusted for age, chronic illness co-morbidity, clinic site, and risk category, were similar to the full model and retained statistical significance for individuals with medium or low quality of life scores (OR=1.47; 95% CI: 1.21-1.78 and OR=1.86; 95% CI: 1.35-2.55, respectively).

The full model for the association between levels of symptom burden and poor adherence also retained statistical significance, but the magnitudes of the associations

were attenuated. Specifically, patients with medium levels of symptom burden had 42% increased odds and patients with high levels had 74% increased odds of poor adherence, compared to patients with low levels of symptom burden (OR=1.42; 95% CI: 1.14-1.75 and OR=1.74; 95% CI: 1.07-2.84, respectively). Findings from the reduced model, adjusted for age, chronic illness co-morbidity, clinic site, and risk category, were similar to the findings in the full model (OR=1.42; 95% CI: 1.14-1.75 and OR=1.75; 95% CI: 1.07-2.85, respectively).

Similar to the unadjusted model, the full model for the physical activity-adherence association indicated a dose-response relationship. As physical activity levels increased, the odds of poor adherence decreased. However, the associations were not statistically significant. Findings from the reduced model, adjusted for age, chronic illness comorbidity, clinic site, and risk factor, were similar to the findings of the full model. Participants with low levels of physical activity had almost 10% decreased odds of poor adherence, compared to participants who were not physically active (OR=0.91; 95% CI: 0.75-1.11). Participants with moderate levels had 21% decreased odds of poor adherence (OR=0.79; 95% CI: 0.60-1.05), and participants with high levels of physical activity had 25% decreased odds of poor adherence (OR=0.75; 95% CI: 0.57-1.00).

4.4 Adjusted Associations Between Patient Reported Outcomes and Adherence Stratified by Clinic Site

Although there were slight differences in the magnitude of the associations between hazardous drinking and poor adherence among different clinic sites, the differences were not statistically significant (test of homogeneity p-value=0.21). Among participants from the Fenway and San Francisco clinics, there was no association between hazardous

drinking and poor adherence (OR=1.05; 95% CI: 0.60-1.86 and OR=1.04; 95% CI: 0.61-1.77, respectively). Among patients from the other five clinics, there was a positive association between hazardous drinking and poor adherence. Among participants at both the Johns Hopkins and Chapel Hill clinics, patients classified as hazardous drinkers had more than twice the odds of poor adherence as compared to those not classified as hazardous drinkers (OR=2.37; 95% CI: 1.01-5.55 and OR=2.36; 95% CI: 1.08-4.64, respectively).

There was no evidence of effect modification by clinic site for the substance use-adherence association (test of homogeneity p-value=0.09). There was no association between past substance use and poor adherence among patients from the University of Washington clinic (OR=1.00; 95% CI: 0.61-1.63). Among participants at the San Francisco clinic, the association between past substance use and poor adherence was negative (OR=0.81; 95% CI: 0.41-1.59). Among participants at the Fenway, Alabama, San Diego, and Chapel Hill clinics, there was a positive association between past substance use and poor adherence.

All clinic sites demonstrated a positive association between current substance use and poor adherence. Among participants at Johns Hopkins, current substance users had almost 13 times the odds of poor adherence, compared to non-users (OR=12.97; 95% CI: 3.21-52.48). Among participants from the UNC-Chapel Hill clinic, current substance users had over seven times the odds of poor adherence (OR=7.55; 95% CI: 2.69-21.16).

Although there were slight differences in the magnitude of the ORs for the depression-adherence association when stratified by clinic site, site was not an effect modifier (test of homogeneity p-value=0.42). For patients reporting mild depressive

symptoms, six of the clinic sites indicated positive associations with poor adherence. The largest in magnitude occurred among patients at the Fenway clinic, with mildly depressed patients having more than twice the odds of poor adherence, compared to patients with no depressive symptoms (OR=2.26; 95% CI: 1.19-4.29). Among patients at the University of Washington clinic, there was no association between mild depression and poor adherence (OR=0.97; 95% CI: 0.56-1.67).

There was a positive association between moderate depressive symptoms and poor adherence among patients from all seven clinic sites. Among participants at Johns Hopkins and the San Diego clinics, those classified as having moderate depressive symptoms had more than three times the odds of poor adherence as compared to those with no depressive symptoms (OR=3.20; 95% CI: 0.71-14.4 and OR=3.07; 95% CI: 2.11-4.49, respectively).

Among participants at the UNC-Chapel Hill clinic, there was a negative association between severe depression and poor adherence (OR=0.74; 95% CI: 0.09-6.52). Among participants from the other six clinics, there was a positive association between severe depression and poor adherence.

Although there were slight differences in the magnitude of the associations between quality of life scores and poor adherence among different clinic sites, the differences were not statistically significant (test of homogeneity p-value=0.44). Among participants at the University of Washington clinic, there was no association between medium quality of life scores and poor adherence as compared to patients with high quality of life scores (OR=0.99; 95% CI: 0.56-1.76). At the other six clinics, there was a positive association between medium quality of life scores and poor adherence. Among patients at Johns

Hopkins, those patients classified as having medium quality of life scores had over five times the odds of poor adherence as compared to patients with high quality of life scores (OR=5.70; 95% CI: 2.01-16.16).

There was a positive association between low quality of life scores and poor adherence among participants at five of the clinic sites. Among participants at the UNC-Chapel Hill clinic, patients with low quality of life scores had over seven times the odds of poor adherence as compared to patients with high quality of life scores (OR=7.28; 95% CI: 1.79-29.69). Among patients at the University of Washington clinic, there was a negative association between low quality of life scores and poor adherence (OR=0.80; 95% CI: 0.31-2.11).

There was no evidence of effect modification by clinic site for the symptom burden-adherence association (test of homogeneity p-value=0.39). Among participants at the University of Washington clinic, there was no association between medium levels of symptom burden and adherence as compared to those patients with low levels of symptom burden (OR=0.99; 95% CI: 0.54-1.82). Among participants at the San Francisco clinic, there was a negative association between medium levels of symptom burden and poor adherence (OR=0.81; 95% CI: 0.44-1.49). Among patients from the Fenway, Alabama, UNC, and San Diego clinics, the association between medium levels of symptom burden and poor adherence was positive.

There was a positive association between high levels of symptom burden and poor adherence among five of the clinic sites. Among participants at the University of Washington clinic, there was no association between high levels of symptom burden and poor adherence as compared to patients with low levels of symptom burden (OR=1.03;

95% CI: 0.35-3.06). Among participants at the Alabama, San Diego, and UNC clinics, patients with high levels of symptom burden had more than twice the odds of poor adherence as compared to patients with low levels of symptom burden (Alabama: OR=2.16; 95% CI: 0.50-9.27, San Diego: OR=2.28; 95% CI: 1.08-4.81, and UNC: OR=2.66; 95% CI: 0.41-17.3).

Although there were slight differences in the magnitude of the associations between physical activity levels and poor adherence among different clinic sites, the differences were not statistically significant (test of homogeneity p-value=0.32). Among participants at the Fenway clinic, there was no association between low levels of physical activity and poor adherence as compared to patients with no physical activity (OR=1.01; 95% CI: 0.50-2.03). Among participants at Johns Hopkins, patients with low levels of physical activity had 2.72 times the odds of poor adherence, compared to patients reporting no physical activity (OR=2.72; 95% CI: 1.10-6.75). Among participants at the remaining five clinics, there was a negative association between low levels of physical activity and poor adherence.

There was a positive association between medium levels of physical activity and poor adherence among patients at both Johns Hopkins and the University of Washington clinics (OR=2.81; 95% CI: 0.73-10.81 and OR=1.22; 95% CI: 0.60-2.49, respectively). Among participants at the Fenway, Alabama, San Diego, San Francisco, and UNC clinics, there was a negative association between medium levels of physical activity and poor adherence as compared to patients that are not physically active.

Among participants at six of the seven clinics, there was a negative association between high levels of physical activity and poor adherence. Among patients at Johns

Hopkins, there was a positive association between high levels of physical activity and poor adherence as compared to patients who reported no physical activity (OR=1.69; 95% CI: 0.39-7.36).

4.5 Adjusted Associations Between Patient Reported Outcomes and Adherence Stratified by Risk Category

There was evidence of effect modification by risk category for the hazardous alcohol use-adherence association (test for homogeneity p-value=0.05). Among injection drug users, hazardous drinkers had almost 75% decreased odds of poor adherence (OR=0.27; 95% CI: 0.03-2.19). The other three categories demonstrated that hazardous alcohol drinking increased the odds of poor adherence. Findings were similar among both the categories of men who have sex with men (MSM) and heterosexual contact (OR=1.46; 95% CI: 1.14-1.87 and OR=1.44; 95% CI: 1.04-2.00, respectively). Among patients in the risk category of other (hemophilia, receipt of blood transfusion, or occupational exposure), hazardous drinkers had over four times the odds of poor adherence (OR=4.34; 95% CI: 1.42-13.23).

Although there were slight differences in the magnitude of the associations between substance use and poor adherence among different risk categories, the differences were not statistically significant (test of homogeneity p-value=0.60). Among participants in the injection drug user or other risk categories, there was a negative association between past substance use and poor adherence as compared to participants who reported no past substance use. Among participants in the MSM or heterosexual risk categories, there was a positive association between past substance use and poor adherence.

Participants in all four risk categories demonstrated a positive association between current substance use and poor adherence. Among patients in the risk categories of heterosexual contact or injection drug use, participants who reported current drug use had three times the odds of poor adherence as compared to participants who reported no drug use (OR=2.95; 95% CI: 1.89-4.60 and OR=3.14; 95% CI: 0.91-10.87, respectively). Among the risk category of MSM, patients who reported current substance use had over four times the odds of poor adherence (OR=4.24; 95% CI: 3.02-5.95).

There was no evidence of effect modification by risk category for the depression-adherence association (test of homogeneity p-value=0.42). There was a positive association between any level of depressive symptoms and poor adherence among all four risk categories. Among participants in the risk category of other, patients who reported mild depressive symptoms had four times the risk of poor adherence as compared to patients who reported no depressive symptoms (OR=4.31; 95% CI: 1.32-14.12). Among participants in the risk categories of injection drug user, MSM, or heterosexual contact, patients who reported moderate depressive symptoms had more than twice the odds of poor adherence as compared to patients who reported no depressive symptoms (IDU: OR=2.43; 95% CI: 0.86-6.86, MSM: OR=2.46; 95% CI: 1.87-3.24, and heterosexual: OR=2.05; 95% CI: 1.42-2.95). Among participants in the risk categories of MSM or heterosexual contact, patients who reported severe depressive symptoms had over 50% increased odds of poor adherence (OR=1.51; 95% CI: 0.89-2.57 and OR=1.66; 95% CI: 0.87-3.17, respectively).

Risk category did not modify the association between quality of life scores and poor adherence (test of homogeneity p-value=0.97). There was a positive association between

lower quality of life scores and poor adherence among all four risk categories. Among participants in the risk categories of MSM or heterosexual contact, patients with medium quality of life scores had almost 50% increased odds of poor adherence, compared to patients with high quality of life scores (OR=1.45; 95% CI: 1.12-1.86 and OR=1.49; 95% CI: 1.05-2.10, respectively). Among participants in those same risk categories (MSM or heterosexual contact), patients with low quality of life scores had approximately twice the odds of poor adherence (OR=1.90; 95% CI: 1.26-2.86 and OR=2.15; 95% CI: 1.20-3.84, respectively).

There was no evidence of effect modification by risk category for the symptom burden-adherence association (test of homogeneity p-value=0.70). There was a positive association between medium levels of symptom burden and poor adherence among all four risk categories. The magnitudes of those associations were similar among injection drug users, heterosexuals, and MSM (OR=1.15; 95% CI: 0.37-3.53, OR=1.44; 95% CI: 0.99-2.08, and OR=1.38; 95% CI: 1.04-1.83, respectively). Among participants in the risk category of other, patients who reported medium levels of symptom burden had almost five times the odds of poor adherence as compared to patients who reported low levels of symptom burden (OR=4.80; 95% CI: 1.31-17.56).

There was no association between high levels of symptom burden and poor adherence among patients in the risk category of other (OR=0.98; 95% CI: 0.08-12.28). Among the risk category of heterosexual contact, patients with high levels of symptom burden had 72% increased odds of poor adherence as compared to patients with low levels of symptom burden (OR=1.72; 95% CI: 0.74-4.02). Among MSM, patients with

high levels of symptom burden had twice the odds of poor adherence (OR=2.09; 95% CI: 1.11-3.94).

Although there were slight differences in the magnitude of the ORs for the physical activity-adherence association when stratified by risk category, risk category was not an effect modifier (test of homogeneity p-value=0.57). Among MSM and the risk category of other, patients who reported low levels of physical activity had decreased odds of poor adherence, compared to patients with no physical activity (OR=0.83; 95% CI: 0.64-1.08 and OR=0.89; 95% CI: 0.28-2.83, respectively). There was no association between low levels of physical activity and adherence among the risk category of heterosexual contact (OR=1.02; 95% CI: 0.73-1.44). Among injection drug users, patients with low levels of physical activity had 27% increased odds of poor adherence as compared to patients with no physical activity (OR=1.27; 95% CI: 0.47-3.43).

Among participants in the risk category of MSM or heterosexual contact, there was a negative association between medium levels of physical activity and poor adherence. Among participants in the risk category of injection drug user or other, there was a positive association between medium levels of physical activity and poor adherence. Among the risk categories of MSM, heterosexual contact, or other, there was a negative association between high levels of physical activity and poor adherence.

4.6 Mediation Analyses

Results for the steps of the mediation analysis that examined the effects of depression and substance use on adherence are displayed in table 6. With regards to the first step of the exposure-outcome association, depression predicted poor adherence (OR=1.87; 95% CI: 1.58-2.20). Findings from step 2 demonstrate that depression (i.e.

the exposure) also predicts the potential mediator, substance use (OR=2.10; 95% CI: 1.81-2.46). Findings from the third step demonstrate that substance use (i.e. the potential mediator) was associated with an increased odds of poor adherence (i.e. the outcome), and the association was statistically significant (OR=1.75; 95% CI: 1.47-2.08). Finally, in the model controlling for substance use, the association between depression and poor adherence retained significance and was attenuated, compared to the model that did not control for substance use (OR=1.72; 95% CI: 1.44-2.05). These findings support the theory that substance use mediated the association between depression and poor adherence.

A similar mediation analysis was conducted to assess whether hazardous alcohol drinking was a mediator in the association between depression and adherence (table 7). Findings from the first step demonstrate that depression (i.e. the exposure) predicted the outcome, poor adherence (OR=1.85; 95% CI: 1.58-2.17). In the second step, the association between depression and hazardous drinking (i.e. the potential mediator) was not statistically significant (OR=1.14; 95% CI: 0.96-1.35). Findings from step three demonstrate that hazardous drinking was associated with an increased odds of poor adherence, and the association was statistically significant (OR=1.55; 95% CI: 1.28-1.87). In the fourth step, the association between depression and poor adherence was slightly attenuated when the model controlled for hazardous drinking and retained statistical significance (OR=1.84; 95% CI: 1.57-2.16). However, in the second step, the exposure (depression) was not statistically significantly associated with the potential mediator (hazardous drinking). Therefore, these findings failed to support the hypothesis

that hazardous alcohol drinking mediated the association between depression and poor adherence.

4.7 Additional Results: Participant Characteristics of Younger Adults, Age 21 to 49

The majority of the population of younger adults was male (87%) and non-Hispanic White (46%) (table 8). Approximately 71% of the population were adherent, and 29% were non-adherent. The adherent and non-adherent groups were similar with respect to gender ($p=0.78$), race/ethnicity ($p=0.28$), risk category ($p=0.13$), and chronic illness co-morbidity ($p=0.22$).

The majority of the population of younger adults were in the oldest age category of 45-49 years (35%). However, there were statistically significant differences in age between the two adherence groups ($p=0.0010$). Among the adherent participants, only 9% were in the youngest age category of 21-29 years, and 36% were in the oldest age category of 45-49 years. In comparison, among the non-adherent group, 14% were age 21-29 years and 32% were in the oldest age category of 45-49 years.

The majority of younger adults received care from the clinics at the University of California-San Diego (28%) and the University of Alabama-Birmingham (23%). The clinic with the smallest number of participants was Johns Hopkins (2%). There were statistically significant differences in clinic sites between the adherent and non-adherent participants ($p<0.0001$). The largest difference among clinic sites was at the University of California-San Francisco. Among the adherent population, 10% were receiving care at the San Francisco clinic. In comparison, among the non-adherent group, 17% were receiving care at that clinic.

Frequencies were statistically significantly different among all of the PROs for the population of younger adults. More of the non-adherent group were classified as hazardous alcohol drinkers (31%) compared to 27% in the adherent group ($p=0.0017$). Similarly, more of the non-adherent group were classified as either past or current substance users ($p<0.0001$). Among adherent participants, 11% reported current substance use. In comparison, among the non-adherent participants, 24% reported current substance use. More of the non-adherent group reported depressive symptoms in all three categories of depression (mild, moderate, and severe; $p<0.0001$). Only 41% of the non-adherent participants reported no depressive symptoms, compared to 59% of the adherent participants.

Also, more of the non-adherent group reported lower health-related quality of life scores ($p<0.0001$). In the adherent group, 18% reported medium quality of life scores and 4% reported low quality of life scores. In comparison, among the non-adherent group, 26% reported medium quality of life scores and 7% reported low quality of life scores. The non-adherent group also reported higher levels of symptom burden ($p<0.0001$) with 21% reporting medium levels of symptom burden and 4% reporting high levels of symptom burden. In comparison, among the adherent group, 12% reported medium levels and 2% reported high levels of symptom burden. The non-adherent group was less physically active than the adherent population, and this difference was also statistically significant ($p<0.0001$). Among the adherent group, 22% reported no physical activity and 15% reported high levels of physical activity. In comparison, among the non-adherent group, 26% reported no physical activity and only 12% reported high levels of physical activity.

4.8 Adjusted Associations Between Patient Reported Outcomes and Adherence among Younger Adults, Age 21 to 49

When adjusted for age, chronic illness co-morbidity, clinic site, risk category, race/ethnicity, and gender, the association between all six patient reported outcomes and poor adherence was statistically significant in the full models and retained significance in the reduced models. Hazardous alcohol drinkers had 1.27 times the odds of poor adherence as compared to non-hazardous drinkers in the full model (OR=1.27; 95% CI: 1.09-1.47) (table 9). In the reduced model, adjusted for age, race/ethnicity, and clinic site, the magnitude was unchanged and the association retained statistical significance (OR=1.27; 95% CI: 1.09-1.47).

Participants who reported past substance use had 24% increased odds of poor adherence (OR=1.24; 95% CI: 1.05-1.47), and patients who reported current substance use had almost three times the odds of poor adherence (OR=2.78; 95% CI: 2.28-3.40), as compared to patients who reported no substance use. In the reduced model, adjusted for age, race/ethnicity, and clinic site, the magnitudes of these associations were slightly attenuated and the model retained statistical significance (past: OR=1.23; 95% CI: 1.04-1.45; current: OR=2.76; 95% CI: 2.27-3.36).

There was a statistically significant dose-response relationship in the association between depressive symptoms and poor adherence in both the full and reduced models. As the level of depressive symptoms increased, the odds of poor adherence increased. Individuals reporting mild depressive symptoms had 68% increased odds of poor adherence as compared to participants who reported no depressive symptoms (OR=1.68; 95% CI: 1.42-2.00). Individuals with moderate depressive symptoms had 2.39 times the

odds of poor adherence (OR=2.39; 95% CI: 2.00-2.85), and individuals with severe depressive symptoms had 2.55 times the odds of poor adherence (OR=2.55; 95% CI: 1.87-3.48). The reduced model was adjusted for age, race/ethnicity, and clinic site. Findings from the reduced model were similar to those in the full model, and retained statistical significance (mild: OR=1.69; 95% CI: 1.43-2.00; moderate: OR=2.38; 95% CI: 2.00-2.84; and severe: OR=2.54; 95% CI: 1.86-3.47).

There was also a dose-response relationship in the association between quality of life scores and poor adherence. As the quality of life score decreased, the odds of poor adherence to HAART increased. Participants with medium quality of life scores had 83% increased odds of poor adherence (OR=1.83; 95% CI: 1.55-2.16), as compared to patients with high quality of life scores. Participants with low quality of life scores had twice the odds of poor adherence (OR=2.19; 95% CI: 1.64-2.93). Magnitudes remained the same in the reduced model (adjusted for age, race/ethnicity, and clinic site) for participants with medium quality of life scores (OR=1.83; 95% CI: 1.55-2.16), and changed very little for participants with low quality of life scores (OR=2.17; 95% CI: 1.62-2.90).

The association between symptom burden and adherence was also statistically significant, and findings from both the full and reduced models demonstrated a dose-response relationship. As symptom burden levels increased, the odds of poor adherence increased. Patients who reported medium levels of symptom burden had 1.93 times the odds of poor adherence (OR=1.93; 95% CI: 1.61-2.32) as compared to patients with low levels of symptom burden. Patients who reported high levels of symptom burden had more than twice the odds of poor adherence (OR=2.13; 95% CI: 1.47-3.09). Findings for

the reduced model were largely unchanged (medium levels: OR=1.93; 95% CI: 1.61-2.32 and high levels: OR=2.12; 95% CI: 1.46-3.07).

There was also a statistically significant dose-response relationship between physical activity levels and poor adherence. As physical activity level increased, the odds of poor adherence decreased. Patients reporting low levels of physical activity had 22% decreased odds of poor adherence as compared to patients reporting no physical activity (OR=0.78; 95% CI: 0.66-0.93). Patients reporting moderate levels of physical activity had 34% decreased odds of poor adherence (OR=0.66; 95% CI: 0.53-0.82), and patients with high levels of physical activity had 35% decreased odds of poor adherence (OR=0.65; 95% CI: 0.52-0.82). The magnitude of the ORs in the reduced model, adjusted for age and clinic site, were similar to the full model and retained statistical significance (low: OR=0.79; 95% CI: 0.66-0.94, moderate: OR=0.67; 95% CI: 0.54-0.82, and high: OR=0.66; 95% CI: 0.52-0.83).

Table 1: Demographic characteristics of study participants age 50 and older

Demographics	Total n=3309 n (%)	Non-Adherent n=817 n (%)	P-value
Gender			0.3504
Male	2808 (84.9)	685 (83.8)	
Female	501 (15.1)	132 (16.2)	
Race / Ethnicity			0.5967
Non-Hispanic White	1796 (54.3)	429 (52.5)	
Non-Hispanic Black/African American	1029 (31.1)	266 (32.6)	
Hispanic	362 (10.9)	94 (11.5)	
Other / Unknown / Missing	122 (5.3)	28 (3.4)	
Age			<.0001
50-54 years	1526 (46.1)	433 (53.0)	
55-59 years	983 (29.7)	226 (27.7)	
60-64 years	501 (15.1)	108 (13.2)	
65-86 years	299 (9.0)	50 (6.1)	
Clinic			<.0001
Univ. California - San Diego	1001 (30.3)	235 (28.8)	
Univ. Alabama - Birmingham	741 (22.4)	172 (21.1)	
Univ. Washington	397 (12.0)	121 (14.8)	
Fenway	328 (9.9)	73 (8.9)	
Univ. California - San Francisco	322 (9.7)	115 (14.1)	
Johns Hopkins	277 (8.4)	51 (6.2)	
Univ. North Carolina - Chapel Hill	243 (7.3)	50 (6.1)	
Risk Category			0.0375
Man who has sex with men	1846 (55.8)	457 (55.9)	
Injection Drug User	176 (5.3)	27 (3.3)	
Heterosexual	1137 (34.4)	292 (35.7)	
Other	102 (3.1)	30 (3.7)	
Missing	48 (1.5)	11 (1.4)	
Chronic Illness Co-morbidity			0.0073
Not Present	1470 (44.4)	396 (48.5)	
Present	1839 (55.6)	421 (51.5)	
Alcohol Use			<.0001
Non-hazardous Drinking	2657 (80.3)	611 (74.8)	
Hazardous Alcohol Drinking	652 (19.7)	206 (25.2)	
Substance Use			<.0001
No Substance Use	1421 (42.9)	278 (34.0)	
Past Substance Use	1144 (34.6)	272 (33.3)	
Current Substance Use	350 (10.6)	172 (21.1)	
Missing	394 (11.9)	95 (11.6)	
Depression			<.0001
No Depressive Symptoms	1867 (56.6)	367 (45.1)	
Mild Depressive Symptoms	740 (22.4)	206 (25.3)	
Moderate Depressive Symptoms	559 (17.0)	202 (24.9)	
Severe Depressive Symptoms	131 (4.0)	38 (4.7)	
Health-related Quality of Life			<.0001
High Health-related Quality of Life	2132 (64.4)	462 (56.6)	
Medium Health-related Quality of Life	712 (21.5)	205 (25.1)	
Low Health-related Quality of Life	193 (5.8)	66 (8.1)	
Missing	272 (8.2)	84 (10.3)	

Symptom Burden			0.0002
Low Symptom Burden	2362 (71.4)	557 (68.2)	
Medium Symptom Burden	507 (15.3)	155 (19.0)	
High Symptom Burden	73 (2.2)	27 (3.3)	
Missing	367 (11.1)	78 (9.6)	
Physical Activity			0.0598
Not Physically Active	912 (27.6)	237 (29.0)	
Low Physical Activity	1273 (38.5)	307 (37.6)	
Moderate Physical Activity	422 (12.8)	94 (11.5)	
High Physical Activity	409 (12.4)	90 (11.0)	
Missing	293 (8.9)	89 (10.9)	

Source: 2014 CNICS data

Table 2: Unadjusted odds ratios of factors associated with poor adherence to HAART of study participants age 50 and older

Variable	Odds Ratio	95% CI
Gender		
Male	referent	
Female	1.11	0.89 - 1.38
Race / Ethnicity		
Non-Hispanic White	referent	
Non-Hispanic Black/African American	1.11	0.93 - 1.33
Hispanic	1.12	0.86 - 1.45
Other / Unknown	0.95	0.61 - 1.47
Age		
50-54 years	referent	
55-59 years	0.75	0.63 - 0.91
60-64 years	0.69	0.55 - 0.88
65-86 years	0.51	0.37 - 0.70
Clinic		
Univ. California - San Diego	referent	
Univ. Alabama - Birmingham	0.99	0.79 - 1.23
Univ. Washington	1.43	1.10 - 1.85
Fenway	0.93	0.69 - 1.26
Univ. California - San Francisco	1.81	1.38 - 2.38
Johns Hopkins	0.74	0.53 - 1.03
Univ. North Carolina - Chapel Hill	0.84	0.60 - 1.19
Risk Category		
Heterosexual	referent	
Injection Drug User	0.52	0.34 - 0.81
Man who has sex with men	0.95	0.80 - 1.13
Other	1.21	0.77 - 1.88
Missing	0.86	0.43 – 1.71
Chronic Illness Co-morbidity		
Not Present	referent	
Present	0.81	0.69 - 0.94

Alcohol Use		
Non-hazardous Drinking	referent	
Hazardous Alcohol Drinking	1.55	1.28 - 1.87
Substance Use		
No Substance Use	referent	
Past Substance Use	1.30	1.07 - 1.58
Current Substance Use	3.98	3.09 - 5.14
Missing	1.32	1.01 - 1.73
Depression		
No Depressive Symptoms	referent	
Mild Depressive Symptoms	1.58	1.30 - 1.92
Moderate Depressive Symptoms	2.31	1.88 - 2.84
Severe Depressive Symptoms	1.67	1.13 - 2.48
Health-related Quality of Life		
High Health-related Quality of Life	referent	
Medium Health-related Quality of Life	1.46	1.21 - 1.77
Low Health-related Quality of Life	1.88	1.37 - 2.57
Missing	1.62	1.22 - 2.13
Symptom Burden		
Low Symptom Burden	referent	
Medium Symptom Burden	1.43	1.16 - 1.76
High Symptom Burden	1.90	1.17 - 3.09
Missing	0.88	0.67 - 1.14
Physical Activity		
Not Physically Active	referent	
Low Physical Activity	0.91	0.74 - 1.10
Moderate Physical Activity	0.82	0.62 - 1.07
High Physical Activity	0.80	0.61 - 1.06
Missing	1.24	0.93 - 1.66

Source: 2014 CNICS data

Table 3: Adjusted odds ratios of patient reported outcomes associated with poor adherence to HAART of study participants age 50 and older[1]

Variable	Full Model Odds Ratio (95% CI)	P-value	Reduced Model Odds Ratio (95% CI)	P-value
Alcohol Use[2]		<0.0001		<0.0001
Non-hazardous Drinking	referent		referent	
Hazardous Alcohol Drinking	1.51 (1.25-1.83)		1.50 (1.24-1.82)	
Substance Use[3]		<0.0001		<0.0001
No Substance Use	referent		referent	
Past Substance Use	1.27 (1.04-1.55)		1.26 (1.04-1.54)	
Current Substance Use	3.82 (2.94-4.95)		3.83 (2.96-4.97)	
Missing	1.34 (1.02-1.77)		1.34 (1.02-1.76)	
Depression[2]		<0.0001		<0.0001
No Depressive Symptoms	referent		referent	
Mild Depressive Symptoms	1.58 (1.30-1.93)		1.57 (1.29-1.92)	
Moderate Depressive Symptoms	2.28 (1.85-2.82)		2.26 (1.83-2.79)	
Severe Depressive Symptoms	1.56 (1.05-2.32)		1.55 (1.04-2.31)	
Health-related Quality of Life (QoL)[2]		<0.0001		<0.0001
High Health-related QoL	referent		referent	
Medium Health-related QoL	1.47 (1.21-1.79)		1.47 (1.21-1.78)	
Low Health-related QoL	1.86 (1.35-2.55)		1.86 (1.35-2.55)	
Missing	1.57 (1.18-2.07)		1.58 (1.19-2.08)	
Symptom Burden[2]		0.0023		0.0023
Low Symptom Burden	referent		referent	
Medium Symptom Burden	1.42 (1.14-1.75)		1.42 (1.14-1.75)	
High Symptom Burden	1.74 (1.07-2.84)		1.75 (1.07-2.85)	
Missing	0.96 (0.72-1.28)		0.98 (0.74-1.30)	
Physical Activity[2]		0.0267		0.0237
Not Physically Active	referent		referent	
Low Physical Activity	0.91 (0.75-1.11)		0.91 (0.75-1.11)	
Moderate Physical Activity	0.80 (0.60-1.05)		0.79 (0.60-1.05)	
High Physical Activity	0.76 (0.57-1.00)		0.75 (0.57-1.00)	
Missing	1.26 (0.94-1.69)		1.26 (0.94-1.69)	

Source: 2014 CNICS data

1. Full models adjusted for age, gender, race/ethnicity, risk factor, and chronic illness co-morbidity
2. Reduced model adjusted for age, chronic illness co-morbidity, clinic site, and risk factor
3. Reduced model adjusted for age, gender, and clinic site

Table 4: Adjusted odds ratios and 95% CIs of patient reported outcomes associated with poor adherence to HAART stratified by clinic site

Variable	Fenway n=328	Johns Hopkins n=277	Univ. Alabama n=741	San Diego n=1001	San Francisco n=322	UNC n=243	Univ. Washington n=397	Test of homogeneity p-value
Alcohol Use[1]								0.21
Non-hazardous Drinking	referent	referent	referent	referent	referent	referent	referent	
Hazardous Drinking	1.05 (0.60-1.86)	2.37 (1.01-5.55)	1.36 (0.89-2.07)	1.89 (1.32-2.70)	1.04 (0.61-1.77)	2.24 (1.08-4.64)	1.31 (0.79-2.16)	
Substance Use[2]								0.09
No Substance Use	referent	referent	referent	referent	referent	referent	referent	
Past Substance Use	1.11 (0.59-2.08)	****	1.11 (0.75-1.63)	1.54 (1.03-2.30)	0.81 (0.41-1.59)	1.52 (0.71-3.29)	1.00 (0.61-1.63)	
Current Substance Use	3.68 (1.62-8.35)	12.97 (3.21-52.48)	3.16 (1.68-5.94)	4.27 (2.38-7.69)	2.49 (1.27-4.87)	7.55 (2.69-21.16)	2.37 (1.21-4.64)	

Table 4: Adjusted odds ratios and 95% CIs of patient reported outcomes associated with poor adherence to HAART stratified by clinic site

Variable	Fenway n=328	Johns Hopkins n=277	Univ. Alabama n=741	San Diego n=1001	San Francisco n=322	UNC n=243	Univ. Washington n=397	Test of homogeneity p-value
Depression[1]								0.42
No Depression	referent	referent	referent	referent	referent	referent	referent	
Mild Depression	2.26 (1.19-4.29)	1.53 (0.63-3.70)	1.49 (0.95-2.35)	1.74 (1.20-2.52)	1.91 (1.08-3.38)	1.09 (0.45-2.61)	0.97 (0.56-1.67)	
Moderate Depression	2.79 (1.41-5.52)	3.20 (0.71-14.4)	2.31 (1.48-3.61)	3.07 (2.11-4.49)	1.09 (0.58-2.02)	2.59 (1.01-6.63)	1.51 (0.87-2.62)	
Severe Depression	2.25 (0.55-9.32)	****	1.90 (0.83-4.36)	1.37 (0.66-2.81)	1.40 (0.53-3.73)	0.74 (0.09-6.52)	1.46 (0.51-4.24)	
Quality of Life[1]								0.44
High Quality of Life	referent	referent	referent	referent	referent	referent	referent	
Medium Quality of Life	1.39 (0.77-2.53)	5.70 (2.01-16.16)	1.68 (1.12-2.54)	1.40 (1.003-1.96)	1.25 (0.69-2.26)	1.34 (0.53-3.42)	0.99 (0.56-1.76)	
Low Quality of Life	2.07 (0.73-5.87)	****	1.93 (0.93-3.98)	1.84 (1.12-3.01)	1.25 (0.42-3.74)	7.28 (1.79-29.69)	0.80 (0.31-2.11)	

Table 4: Adjusted odds ratios and 95% CIs of patient reported outcomes associated with poor adherence to HAART stratified by clinic site

Variable	Fenway n=328	Johns Hopkins n=277	Univ. Alabama n=741	San Diego n=1001	San Francisco n=322	UNC n=243	Univ. Washington n=397	Test of homogeneity p-value
Symptom Burden[1]								0.39
Low Symptom Burden	referent	referent	referent	referent	referent	referent	referent	
Medium Symptom Burden	1.43 (0.72-2.85)	****	1.28 (0.80-2.05)	1.95 (1.38-2.75)	0.81 (0.44-1.49)	1.07 (0.34-3.43)	0.99 (0.54-1.82)	
High Symptom Burden	1.11 (0.11-11.08)	****	2.16 (0.50-9.27)	2.28 (1.08-4.81)	1.57 (0.38-6.56)	2.66 (0.41-17.3)	1.03 (0.35-3.06)	
Physical Activity[1]								0.32
No Phys. Activity	referent	referent	referent	referent	referent	referent	referent	
Low Phys. Activity	1.01 (0.50-2.03)	2.72 (1.10-6.75)	0.75 (0.49-1.15)	0.91 (0.64-1.28)	0.69 (0.37-1.26)	0.81 (0.35-1.86)	0.92 (0.53-1.58)	
Med. Phys. Activity	0.80 (0.34-1.89)	2.81 (0.73-10.81)	0.45 (0.24-0.87)	0.92 (0.56-1.52)	0.45 (0.20-1.02)	0.71 (0.24-2.12)	1.22 (0.60-2.49)	
High Phys. Activity	0.63 (0.25-1.59)	1.69 (0.39-7.36)	0.75 (0.41-1.37)	0.76 (0.46-1.24)	0.93 (0.40-2.13)	0.28 (0.07-1.14)	0.68 (0.32-1.43)	

Source: 2014 CNICS data

****ORs could not be calculated due to very small cells

1. Reduced model adjusted for age, chronic illness co-morbidity, clinic site, and risk factor

2. Reduced model adjusted for age, gender, and clinic site

Table 5: Adjusted odds ratios and 95% CIs of patient reported outcomes associated with poor adherence to HAART stratified by risk category

Variable	Injection Drug User n=176	MSM n=1846	Heterosexual n=1137	Other n=102	Test of Homogeneity p-value
Alcohol Use[1]					0.05
Non-hazardous Drinking	referent	referent	referent	referent	
Hazardous Drinking	0.27 (0.03-2.19)	1.46 (1.14-1.87)	1.44 (1.04-2.00)	4.34 (1.42-13.23)	
Substance Use[2]					0.60
No Substance Use	referent	referent	referent	referent	
Past Substance Use	0.35 (0.09-1.41)	1.41 (1.08-1.83)	1.16 (0.83-1.62)	0.77 (0.22-2.70)	
Current Substance Use	3.14 (0.91-10.87)	4.24 (3.02-5.95)	2.95 (1.89-4.60)	14.14 (2.63-75.88)	
Depression[1]					0.42
No Depression	referent	referent	referent	referent	
Mild Depression	1.25 (0.45-3.51)	1.70 (1.31-2.21)	1.27 (0.90-1.81)	4.31 (1.32-14.12)	
Moderate Depression	2.43 (0.86-6.86)	2.46 (1.87-3.24)	2.05 (1.42-2.95)	3.30 (1.03-10.53)	
Severe Depression	****	1.51 (0.89-2.57)	1.66 (0.87-3.17)	****	

Table 5: Adjusted odds ratios and 95% CIs of patient reported outcomes associated with poor adherence to HAART stratified by risk category

Variable	Injection Drug User n=176	MSM n=1846	Heterosexual n=1137	Other n=102	Test of Homogeneity p-value
Quality of Life[1]					0.97
High Quality of Life	referent	referent	referent	referent	
Medium Quality of Life	1.25 (0.42-3.70)	1.45 (1.12-1.86)	1.49 (1.05-2.10)	2.83 (0.87-9.22)	
Low Quality of Life	1.35 (0.26-7.08)	1.90 (1.26-2.86)	2.15 (1.20-3.84)	1.12 (0.09-13.49)	
Symptom Burden[1]					0.70
Low Symptom Burden	referent	referent	referent	referent	
Medium Symptom Burden	1.15 (0.37-3.53)	1.38 (1.04-1.83)	1.44 (0.99-2.08)	4.80 (1.31-17.56)	
High Symptom Burden	****	2.09 (1.11-3.94)	1.72 (0.74-4.02)	0.98 (0.08-12.28)	

Table 5: Adjusted odds ratios and 95% CIs of patient reported outcomes associated with poor adherence to HAART stratified by risk category

Variable	Injection Drug User n=176	MSM n=1846	Heterosexual n=1137	Other n=102	Test of Homogeneity p-value
Physical Activity[1]					0.57
No Phys. Activity	referent	referent	referent	referent	
Low Phys. Activity	1.27 (0.47-3.43)	0.83 (0.64-1.08)	1.02 (0.73-1.44)	0.89 (0.28-2.83)	
Med. Phys. Activity	1.66 (0.42-6.59)	0.79 (0.56-1.13)	0.64 (0.38-1.06)	2.14 (0.40-11.45)	
High Phys. Activity	****	0.77 (0.54-1.10)	0.68 (0.41-1.13)	0.52 (0.10-2.83)	

Source: 2014 CNICS data

**** ORs could not be calculated due to very small cells

1. Reduced model adjusted for age, chronic illness co-morbidity, clinic site, and risk factor
2. Reduced model adjusted for age, gender, and clinic site

Table 6: Degree to which substance use mediates association between depression and poor adherence

Logistic Regression	OR (95% CI)
Depression predicting poor adherence	1.87 (1.58 – 2.20)
Depression predicting substance use	2.10 (1.81 – 2.46)
Substance use predicting poor adherence	1.75 (1.47 – 2.08)
Depression predicting poor adherence, controlling substance use	1.72 (1.44 – 2.05)

Source: 2014 CNICS data

Table 7: Degree to which hazardous alcohol use mediates association between depression and poor adherence

Logistic Regression	OR (95% CI)
Depression predicting poor adherence	1.85 (1.58 – 2.17)
Depression predicting hazardous alcohol use	1.14 (0.96 – 1.35)
Hazardous alcohol use predicting poor adherence	1.55 (1.28 – 1.87)
Depression predicting poor adherence, controlling hazardous alcohol use	1.84 (1.57 – 2.16)

Source: 2014 CNICS data

Table 8: Demographic characteristics of study participants age 21-49

Demographics	Total n=4127 n (%)	Non-Adherent n=1214 n (%)	P-value
Gender			0.7794
Male	3538 (85.6)	1043 (85.9)	
Female	589 (14.3)	171 (14.1)	
Race / Ethnicity			0.2794
Non-Hispanic White	1901 (46.1)	538 (44.3)	
Non-Hispanic Black/African American	1207 (29.3)	378 (31.1)	
Hispanic	772 (18.7)	221 (18.2)	
Other / Unknown / Missing	247 (6.0)	77 (6.3)	
Age			0.0010
21-29 years	438 (10.6)	164 (13.5)	
30-34 years	594 (14.4)	170 (14.0)	
35-39 years	735 (17.8)	226 (18.6)	
40-44 years	935 (22.7)	269 (22.2)	
45-49 years	1425 (34.5)	385 (31.7)	
Clinic			<0.0001
Univ. California - San Diego	345 (28.4)	345 (28.4)	
Univ. Alabama - Birmingham	275 (22.7)	275 (22.7)	
Univ. Washington	193 (15.9)	193 (15.9)	
Fenway	96 (7.9)	96 (7.9)	
Univ. California - San Francisco	203 (16.7)	203 (16.7)	
Johns Hopkins	25 (2.1)	25 (2.1)	
Univ. North Carolina - Chapel Hill	77 (6.3)	77 (6.3)	
Risk Category			0.1317
Man who has sex with men	2684 (65.0)	807 (66.5)	
Injection Drug User	75 (1.8)	20 (1.7)	
Heterosexual	1196 (29.0)	332 (27.4)	
Other	109 (2.6)	29 (2.4)	
Missing	63 (1.5)	26 (2.1)	
Chronic Illness Co-morbidity			0.2206
Not Present	2926 (70.9)	877 (72.2)	
Present	1201 (29.1)	337 (27.8)	
Alcohol Use			0.0017
Non-hazardous Drinking	2972 (72.0)	833 (68.6)	
Hazardous Alcohol Drinking	1155 (28.0)	381 (31.4)	
Substance Use			<0.0001
No Substance Use	1800 (43.6)	445 (36.7)	
Past Substance Use	1268 (30.7)	356 (29.3)	
Current Substance Use	615 (14.9)	291 (24.0)	
Missing	444 (10.8)	122 (10.1)	
Depression			<0.0001
No Depressive Symptoms	2215 (53.7)	501 (41.3)	
Mild Depressive Symptoms	951 (23.0)	313 (25.8)	
Moderate Depressive Symptoms	767 (18.6)	314 (25.9)	
Severe Depressive Symptoms	182 (4.4)	79 (6.5)	
Missing	12 (0.3)	7 (0.6)	

Health-related Quality of Life			<0.0001
High Health-related Quality of Life	2823 (68.4)	726 (59.8)	
Medium Health-related Quality of Life	831 (20.1)	314 (25.9)	
Low Health-related Quality of Life	208 (5.0)	87 (7.2)	
Missing	265 (6.4)	87 (7.2)	
Symptom Burden			<0.0001
Low Symptom Burden	3147 (76.2)	840 (69.2)	
Medium Symptom Burden	607 (14.7)	249 (20.5)	
High Symptom Burden	121 (2.9)	53 (4.4)	
Missing	253 (6.1)	72 (5.9)	
Physical Activity			<0.0001
Not Physically Active	958 (23.2)	321 (26.4)	
Low Physical Activity	1572 (38.1)	448 (36.9)	
Moderate Physical Activity	771 (18.7)	197 (16.2)	
High Physical Activity	585 (14.2)	147 (12.1)	
Missing	241 (5.8)	101 (8.3)	

Source: 2014 CNICS data

Table 9. Adjusted odds ratios of patient reported outcomes associated with poor adherence to HAART of study participants age 21-49[1]

Variable	Full Model Odds Ratio (95% CI)	P-value	Reduced Model Odds Ratio (95% CI)	P-value
Alcohol Use[2]				
Non-hazardous Drinking	referent		referent	
Hazardous Alcohol Drinking	1.27 (1.09-1.47)		1.27 (1.09-1.47)	
Substance Use[2]				
No Substance Use	referent		referent	
Past Substance Use	1.24 (1.05-1.47)		1.23 (1.04-1.45)	
Current Substance Use	2.78 (2.28-3.40)		2.76 (2.27-3.36)	
Missing	1.22 (0.96-1.56)		1.21 (0.95-1.55)	
Depression[2]				
No Depressive Symptoms	referent		referent	
Mild Depressive Symptoms	1.68 (1.42-2.00)		1.69 (1.43-2.00)	
Moderate Depressive Symptoms	2.39 (2.00-2.85)		2.38 (2.00-2.84)	
Severe Depressive Symptoms	2.55 (1.87-3.48)		2.54 (1.86-3.47)	
Health-related Quality of Life (QoL)[2]				
High Health-related QoL	referent		referent	
Medium Health-related QoL	1.83 (1.55-2.16)		1.83 (1.55-2.16)	
Low Health-related QoL	2.19 (1.64-2.93)		2.17 (1.62-2.90)	
Missing	1.38 (1.05-1.81)		1.36 (1.04-1.79)	

Symptom Burden[2]		
Low Symptom Burden	referent	referent
Medium Symptom Burden	1.93 (1..61-2.32)	1.93 (1.61-2.32)
High Symptom Burden	2.13 (1.47-3.09)	2.12 (1.46-3.07)
Missing	1.26 (0.94-1.69)	1.25 (0.94-1.67)
Physical Activity[3]		
Not Physically Active	referent	referent
Low Physical Activity	0.78 (0.66-0.93)	0.79 (0.66-0.94)
Moderate Physical Activity	0.66 (0.53-0.82)	0.67 (0.54-0.82)
High Physical Activity	0.65 (0.52-0.82)	0.66 (0.52-0.83)
Missing	1.44 (1.08-1.93)	1.44 (1.08-1.93)

Source: 2014 CNICS data

1. Full models adjusted for age, gender, race/ethnicity, risk factor, and chronic illness co-morbidity
2. Reduced model adjusted for age, race/ethnicity, and clinic site
3. Reduced model adjusted for age and clinic site

CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS

5.1 Summary of Findings

Although several studies have examined the relationship between individual patient characteristics and medication adherence among people living with HIV, few of those studies have examined those associations in older adults living with HIV. This study's findings indicate that several patient reported outcomes are associated with poor medication adherence among persons aged 50 years and older, who are living with HIV in the U.S. Hazardous alcohol drinkers, past substance users, and current substance users had statistically significant increased odds of poor adherence to HAART. Depression, lower quality of life scores, and higher levels of symptom burden were also associated with statistically significant increased odds of poor adherence. In contrast, higher physical activity levels were associated with decreased odds of poor adherence.

The findings from the current study support the hypothesis that individuals who are classified as hazardous drinkers will have increased odds of poor adherence to a HAART regimen. The current study had similar findings to other studies in the available literature. The Williams study found that about 22% of the population of older HIV-positive adults reported mild to severe unhealthy drinking (Williams et al, 2014). Findings from the current study are consistent with the Williams study, with almost 20% of the population of older HIV-positive adults being classified as hazardous alcohol drinkers. Catz and colleagues found a statistically significant association between alcohol use and adherence, with alcohol drinkers having 12% lower odds of optimal adherence

(OR=0.88; 95% CI: 0.79-0.98) (Catz, 2001). The current study's findings are consistent with the findings in the Catz study. However, the results from the current study indicate a greater magnitude in that association when restricting the evaluation of that association to hazardous alcohol use, instead of any recent alcohol use. The current study found that older adults who are hazardous alcohol drinkers have 33% lower odds of proper treatment adherence, compared to older adults who are not hazardous drinkers. Among younger adults (age 18-50 years) in the CNICS study population, hazardous drinkers have 21% lower odds of proper treatment adherence, suggesting that older adults who are hazardous alcohol drinkers may be at higher risk for poor adherence than younger adults who are hazardous drinkers.

The findings from this study also support the hypothesis that individuals with current or past substance use will have increased odds of poor adherence to a HAART regimen. Similar to the Parsons study of older HIV-positive adults in New York City, the current study found statistically significant increased odds of poor adherence among participants who reported substance use (Parsons et al, 2014). Findings from the current study are also consistent with both the Jeevanjee and Cohn studies. Jeevanjee and colleagues examined the association between illicit substance use and poor adherence among 258 adults living with HIV, and found that illicit substance users had twice the odds of poor adherence (OR=2.10; 95% CI: 1.53-2.87) (Jeevanjee et al, 2014). Cohn and colleagues also found that participants who reported substance use (cocaine, amphetamine, or heroin) had twice the odds of poor adherence (Cohn, 2011). The magnitude of the increase in odds was two-fold in both the Cohn and Jeevanjee studies; however, the magnitude of the increase in odds of poor adherence in the current study was almost four-fold. The difference in

findings between the current study and these two prior studies could be due to the difference in age ranges. The two prior studies were not restricted to older adults.

When the associations between substance use and adherence were evaluated among adults age 18-50 in the CNICS data set, the association for past substance use was very similar to the results of that evaluation for older adults (OR=1.23; 95% CI: 1.04-1.46 and OR=1.26; 95% CI: 1.04-1.54, respectively). However, the magnitude of the association was greater among the population of older adults when evaluating current substance use. Older adults who reported current substance use had 3.83 times the odds of poor adherence, compared to older adults who reported no substance use. In contrast, younger adults who reported current substance abuse had 2.78 times the odds of poor adherence. The findings from the current study may indicate that older adults who use substances may be at even greater risk of poor adherence than the younger population of adults living with HIV who use illicit substances.

The results from the current study also support the hypothesis that individuals with depressive symptoms will have increased odds of poor adherence to a HAART regimen. Similar to the Bianco and Frain studies that were conducted in patients age 50 years and older, this study also found that depressive symptoms were statistically significantly associated with poor adherence (Bianco et al, 2011; Frain et al, 2014). The Bianco study stratified by sex and found that the association between depressive symptoms and poor adherence was only significant for the population of older men. When stratified by sex in the current study, the association between depressive symptoms and poor adherence was statistically significant for both males ($p<0.0001$) and females ($p=0.0010$) (data not shown in table).

Findings from the current study were also consistent with some of the findings of the Wagner study on depression (Wagner, 2011). Wagner and colleagues evaluated the association between depression and adherence among 1,374 HIV-positive patients from 14 sites across the U.S. That study found that individuals with severe depressive symptoms had almost 50% lower odds of proper adherence compared to individuals without depressive symptoms (OR=0.51; 95% CI: 0.34-0.78). The Wagner study also found that individual with mild or moderate depressive symptoms had over 25% decreased odds of proper adherence (OR=0.73; 95% CI: 0.53-1.02), but the association was not statistically significant. Consistent with the Wagner study, the current study found statistically significant increased odds of poor adherence among patients with severe depressive symptoms. Unlike the Wagner study, however, the findings from the current study demonstrated that the associations between mild or moderate depressive symptoms and poor adherence were also statistically significant. This difference in findings could be due to the difference in age ranges. The Wagner study was not restricted to evaluating these associations among older adults.

When comparing the findings in this study of older adults to the population of younger adults in the CNICS data set, the depression-adherence associations were similar for patients with mild or moderate depressive symptoms. Findings did differ with respect to severe depressive symptoms. Adults less than age 50 with severe depressive symptoms had 2.55 times the odds of poor adherence, and adults age 50 and older with severe depressive symptoms had 1.55 times the odds of poor adherence. Among older adults, the association may be weaker than expected among those with severe depressive symptoms due to the very small number of older adults in the exposed population who

were classified as having severe depressive symptoms (n=38). This may have resulted from older adults in the study population not reporting accurate levels of depressive symptoms, thereby being classified as having moderate depressive symptoms, instead of severe depressive symptoms. In conclusion, the hypothesis that older HIV-positive adults with depressive symptoms are at greater risk of non-adherence is supported by the current study, but that association may not be stronger for older adults, in comparison to younger adults.

Most of the studies in the available literature that evaluated associations between quality of life and adherence among patients living with HIV have examined the influence that better adherence may have on quality of life measures. The current study explored the possibility that measures of quality of life may also be used to assess the risk of poor adherence. Findings from this study support the hypothesis that lower scores on the Quality of Life survey will have increased odds of poor adherence to a HAART regimen. Only one other study was found that evaluated such an association between health-related quality of life and HAART adherence (Penedo et al, 2003), and the findings from the current study are consistent with the findings in the Penedo study. That study did not provide odds ratios of the association, but did find that higher scores on a health-related quality of life scale was associated with better medication adherence, and the association was statistically significant ($p<0.01$). Results from the current study also demonstrate a statistically significant association between health-related quality of life scores and adherence.

There have been other studies that have evaluated the association between quality of life scores and medication adherence among older adults receiving treatment for other

chronic illnesses, such as hypertension. One such study was conducted by Holt and colleagues, and the results from the current study are consistent with the findings in the Holt study (Holt et al, 2010). Holt found that patients with low quality of life scores had 33% increased odds of poor adherence than those with medium or high quality of life scores (OR=1.33; 95% CI: 1.01-1.74).

In a comparison of the results for older adults in the current study to those of adults age 18 to 50 in the CNICS data set, the magnitude of the association between quality of life scores and adherence among older adults was less than that of younger adults. Older adults with medium quality of life scores had 47% increased odds of poor adherence, whereas younger adults with medium scores had 84% increased odds of poor adherence, compared to patients with high scores. Older adults with low scores had 86% increased odds of poor adherence, whereas younger adults had more than twice the odds of poor adherence, compared to adults with high scores. These findings suggest that the association between quality of life scores and adherence may be greater for younger adults living with HIV.

The results from the current study support the hypothesis that older HIV-positive adults who report higher levels of symptom burden will have increased odds of poor adherence. These findings were consistent with the findings of the Gonzales study, which found that a greater number of symptoms had a statistically significant association with poor adherence (Gonzalez et al, 2007.) The magnitude of the association between symptom burden and adherence was greater among younger adults in the CNICS data set. For example, older adults with high levels of symptom burden had 1.75 times the odds of poor adherence compared to older adults with low levels of symptom burden. However,

younger (age 18-50) patients with high levels of symptom burden had twice the odds of poor adherence. These findings suggest that the association between symptom burden and adherence may be greater for younger adults living with HIV.

Although the results from the current study support the hypothesis that older adults who are more physically active will have decreased odds of poor adherence to a HAART regimen, the association was not statistically significant. In the Blashill study of data from CNICS, the association between these two variables was statistically significant ($p=0.009$) (Blashill et al, 2013). However, the Blashill study was not restricted to older adults and was restricted to the population of men who have sex with men.

Results from the analysis of the physical activity-adherence association were similar in both the populations of younger adults (age 18-50) and older adults (age 50 and older) in the current study. Specifically, increasing levels of physical activity were associated with decreased odds of poor adherence. However, the association was only statistically significant for the population of younger adults, which is consistent with the findings of the Blashill study.

Clinic site was not an effect modifier for the association between these PROs and poor medication adherence. Stratified analyses did highlight some differences in the associations, but the tests for homogeneity in each of the models were not statistically significant. In all of the models, the ORs overlapped when comparing findings among the different clinic sites.

Risk category was an effect modifier for the association between hazardous alcohol use and poor adherence. Among the risk categories of MSM, heterosexual contact, and other (hemophilia, receipt of blood transfusion, or occupational exposure), hazardous

alcohol use was associated with statistically significant increased odds of poor adherence. However, among participants in the risk category of injection drug use, hazardous drinkers had decreased odds of poor adherence. Although the OR was in the opposite direction from the findings for the other risk categories, it was not statistically significant. It cannot be ruled out that this finding was a spurious one. Risk category was not an effect modifier for any of the other PRO-adherence associations.

For differences among the clinic sites, the two clinics with the smallest sample sizes (Johns Hopkins and UNC-Chapel Hill) were usually the clinics with magnitudes that were much larger than the other five clinics. The same is true for the differences seen in the stratified analyses by risk category. The two risk categories with the smallest sample sizes (injection drug use and other) were usually the categories with the magnitudes that differed the most from the categories with larger sample sizes. If sample sizes were increased at these two clinic sites or in these two risk categories, the findings may be closer to the findings from the other clinic sites and risk categories.

Findings from the first mediation analysis did support the theory that substance use mediated the association between depression and poor adherence. The analysis, however, did not indicate perfect mediation, which would hold if depression had no effect on adherence when controlling for substance use (Baron & Kenny, 1986). The mediation analysis demonstrates that depression can affect substance use which may then affect medication adherence. However, substance use is not necessary for depression to affect medication adherence. Findings from the second mediation analysis did not support the theory that hazardous alcohol use mediated the association between depression and poor

adherence, due to the finding that there was no statistically significant association between depression and hazardous alcohol use.

5.2 Strengths and Limitations

Some limitations of the study should be considered when interpreting the results. The results of the study can only be generalized to the population of older adults receiving medical care in major U.S. urban areas. Factors may be different in rural areas. Furthermore, the study population does not include representation from the Midwest region of the U.S. Since the study only includes patients already enrolled in a research project and receiving medical care, selection bias is a possibility.

Due to the use of self-reported surveys, there is also the possibility for information bias. Individuals may report better adherence rates than their actual behavior, due to a reluctance to disclose behaviors that patients believe would disappoint the healthcare provider. Similarly, patients may under-report levels of alcohol or substance use for the same reason. Furthermore, study participants may over-report healthy behaviors, such as physical activity levels, in order to give more socially desirable responses. The frequency of errors should be approximately the same for both groups (adherent or non-adherent), which may result in nondifferential misclassification and bias results toward the null. Therefore, the true associations may be stronger than observed.

Also, the data do not include other factors that may influence medication adherence and the exposure variables. For example, the CNICS project does not collect data on the presence or type of health insurance coverage, education levels, income levels, time since HIV diagnosis, length of time on HAART, or social support characteristics. As a result,

endogeneity may have occurred, and the observed effects may be due to the effects of unmeasured variables that are associated with both adherence and the exposure variables.

Finally, although statistically significant associations were observed between many of the PROs and poor adherence, the analyses and the theoretical model cannot be used to determine causality. Some of the exposure variables in the analyses, such as quality of life and symptom burden, could also be evaluated as possible outcomes that are impacted by levels of adherence. For example, as adherence levels improve, symptom burden may decrease due to the effectiveness of HAART.

Despite these limitations, the current study has a number of strengths. These strengths include the use of recent, pooled data from multiple clinic sites from different regions of the U.S. and the large number of study participants. In addition, the study evaluated these associations among the population of older adults living with HIV, a growing population and one in which there is sparse research regarding medication adherence. Other strengths include the use of reliable and valid measures to collect data on the exposure and outcome variables, as well as separating out the exposure variables of alcohol use and substance use with two different models. Furthermore, most of the studies on HAART adherence occurred before the widespread use of single tablet regimens, and the strengths of the observed associations in those studies may have been affected by the complexity of the treatment regimen.

5.3 Suggestions for Future Studies

The data available from the CNIC project only allow researchers to evaluate the association between medication adherence and some of the individual characteristics that constitute part of the Andersen Behavioral Model of Health Services Use (Andersen,

1995). The collection and analysis of other components of the model may affect some of the findings from this study. For example, predisposing factors such as social support, level of education, and health beliefs or enabling characteristics such as income and insurance status may have confounding effects on the associations observed in this study. Furthermore, the inclusion of additional clinic sites with more regional representation would allow researchers to assess the influence that regional differences may have on these associations. If regional differences are apparent, then policies and environmental characteristics should be further explored as factors that may play a role with adherence levels on an individual basis. Of particular interest for this population would be environmental components such as the presence of geriatric nurses working in partnership with these infectious disease clinics or qualitative data on patient/provider relationships.

Although differences in the associations between adherence and the patient reported outcomes were not significantly different by clinic site, the unadjusted associations with adherence did show that the San Francisco and Washington clinics had increased odds of poor adherence, compared to the San Diego clinic. Therefore, future studies should evaluate clinic or population differences at these locations. For example, investigators may want to explore the association between adherence and the housing status of patients. Another suggestion for future study would be to conduct a stratified analysis by type of substance when evaluating the association between adherence and substance use. The current study combined cocaine, amphetamine, or opiate use. With sufficient sample size, a study could be conducted that would evaluate associations with particular substances and multiple substance use. Although the current study allowed comparisons

between the population of older adults and younger adults, a stratified analysis by age groups could not be conducted due to the small number of individuals in the older age categories. As the population of people living with HIV continues to increase in these older age categories, such a stratified analysis would provide more detailed information that could support the use of particular interventions for particular age groups.

Longitudinal analyses of CNICS data are also recommended. Such analyses would enable researchers to determine if these observations remained consistent over time. Findings from longitudinal studies could also be used to evaluate the influence that changes in the patient-reported outcomes have on levels of adherence. For example, a study that analyzed the effect of reductions in levels of depression over time on medication adherence would greatly contribute to the literature on this population.

Furthermore, longitudinal studies could be used to examine the differences observed between the older and younger populations. The older population had smaller magnitudes of association between some of the PROs and adherence (i.e. quality of life and symptom burden) and larger magnitudes of association between other PROs and adherence (i.e. hazardous alcohol use and current substance use). As the younger population ages into the older age groups, longitudinal studies could determine if this pattern remains consistent, and the impact of the PROs change over time. For example, a longitudinal study could examine if the magnitude of association between substance use and poor adherence increases as patients age. Also, if new survey tools are created or if current survey tools are shortened as a result of the findings from this study, those tools would need to be assessed for reliability and validity.

5.4 Implications of Research Findings

Research findings from the current study may provide key screening tools for health care providers to assess the risk of poor medication adherence among older patients. Medical providers may want to use one or more of the survey tools from this study with a dual purpose, such as the PHQ-9 to assess for the risk of both depression and poor adherence. Furthermore, a simple survey tool could be developed with the three questions from the AUDIT-C, the nine questions from the PHQ-9, and questions about current substance use from the ASSIST. The results from such a survey tool would provide assessments for the risks of depression, hazardous alcohol use, substance use, and poor medication adherence.

For patients who score high in one or more of these areas, health care providers can then refer those patients to additional services that address those needs, such as substance abuse counseling. In addition, providers can use the responses to this survey to take additional steps to address the risk of poor adherence, such as referring those patients to HIV medical case management or adherence counseling. Furthermore, there are clinical trials being conducted on the development and use of longer lasting HAART regimens, such as one-month and three-month injectables. Patients who are identified as high risk for poor adherence could then be prioritized to receive these new regimens. Providers may also want to discuss the use of Pre-Exposure Prophylaxis (PrEP) by the sex partners of patients who are at high risk of poor adherence. PrEP is a once-daily pill regimen that can reduce the risk of becoming infected with HIV.

Research findings from this study may improve HAART medication adherence among older patients living with HIV, leading to improvements in viral suppression and

better health outcomes among this population. Additionally, improvements in adherence among older patients may also help reduce the costs of HIV care. A recent study by Krentz and Gill found that the mean cost per person, per month (PPPM) was greater for HIV-positive adults over the age of 50, compared to HIV-positive patients age 16-50 (Krentz & Gill, 2015). For older patients, the PPPM was $1,325. For patients less than age 50, the PPPM was $1,075. More complex medication regimens accounted for some of this cost difference, and poor adherence can lead to drug resistance which then causes the medication regimen to become more complex. Ultimately, the findings from this study may lead to more patients experiencing viral suppression, which may then reduce the number of new HIV infections.

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