ALCOHOL USE, HIV INFECTION, AND ANTIRETROVIRAL ADHERENCE

by

Lauren Matukaitis Broyles

Bachelor of Arts, Psychology, St. Mary's College of Maryland, 1995

Bachelor of Science, Nursing, Johns Hopkins University, 1998

Submitted to the Graduate Faculty of

School of Nursing in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

SCHOOL OF NURSING

This dissertation was presented

by

Lauren Matukaitis Broyles

It was defended on

July 30, 2008

and approved by

Judith Erlen, PhD, RN, School of Nursing, Health Promotion and Development

Christopher Ryan, PhD, School of Medicine

Susan Sereika, PhD, Center for Research & Evaluation, School of Nursing

Adam Gordon, MD, MPH, School of Medicine & VA Pittsburgh Healthcare System

Dissertation Advisor: Judith Erlen, PhD, RN, FAAN, School of Nursing,

Health Promotion and Development

ALCOHOL USE, HIV INFECTION, AND ANTIRETROVIRAL ADHERENCE

Lauren Matukaitis Broyles, PhD

University of Pittsburgh, 2008

Alcohol use appears to negatively impact antiretroviral (ART) adherence, though conclusions about its effects are inconsistent, and the mechanisms of these effects are unclear. Accurate assessment of alcohol use is important for adherence counseling in HIV/AIDS. This secondary data analysis aimed to 1) determine if positive alcohol screening tests can predict ART adherence; 2) compare the effects of two ART adherence interventions with usual care across alcohol screening status; 3) explore mediation by self-efficacy in the relationship between adherence and several psychosocial variables; and 4) evaluate the psychometric properties and factor structure of the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C). The sample included 310 HIV+ adults on ART.

Over 25% of the sample was AUDIT-C positive. Through sequential multiple linear regression analyses, AUDIT-C status (but not AUDIT-3 status) significantly added to the prediction of dose adherence (p=.005) and days under-dosing (p=.021) after controlling for confounders and covariates. In repeated measures analysis to determine if alcohol use impacts the effect of the interventions on dose adherence over time, only main effects for time and alcohol screening status were significant. Adherence was significantly lower at Time 2 than at baseline, F (1, 236.287) = 25.595, p = .000, and significantly lower for AUDIT-C positive individuals than for AUDIT-C negative individuals, F (1, 340.338) = 12.304, p = .001. In path analysis, near-significant results suggest partial mediation of the relationship between adherence and conscientiousness by self-efficacy. The internal consistency and test-retest reliability of the

AUDIT-C were high. Multi-sample confirmatory factor analysis revealed factor invariance for sex, but the best-fitting model for race allowed partial invariance where AUDIT-C item 3 (episodic heavy drinking) was free to vary across whites/nonwhites, X^2 (3, 310) = 1.818, p = .6111. Inconsistent AUDIT-C data and missing Time 2 adherence data were significantly related to baseline opioid use.

In conclusion, positive AUDIT-C status may serve as an indirect indicator for ART nonadherence. The AUDIT-C appears to reliably assess alcohol use in PWHIV, but common modifications may risk compromising validity, particularly in drug users. Further attention to the cultural equivalence of the AUDIT-C across racial groups may be warranted.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I would like to formally acknowledge the support of the many individuals who made the completion of this work possible, starting with my committee members. Many, many thanks go to Dr. Judith Erlen for her six years of guidance and encouragement, for so graciously sharing her data, and for serving as the Mentor for my pre-doctoral fellowship support. I also appreciate the guidance of Christopher Ryan in the development and planning of my fellowship proposal, his support as Co-mentor, and for particular attention to the psychosocial dimensions of this project. I owe a significant measure of gratitude to Dr. Susan Sereika for sharing hour after hour of patient, individualized statistical assistance and direction. Dr. Adam Gordon has enthusiastically helped focus the project towards translation to clinical practice, and will help bridge this work into post-doctoral study.

I also need to extend the most sincere thanks to:

the many parent study staff members who provided me with assistance, particularly Project Director Lisa Tamres, and the study participants who shared the experience of living with HIV/AIDS;

Dr. Mary Beth Happ and Dr. Lisa Parker for giving me innumerable opportunities to shine and for helping me integrate a wide range of interdisciplinary interests;

the staff at Interplay Child Care Center and the Second United Presbyterian Church for giving me the peace of mind in knowing that my children were lovingly cared for;

my father, John, my stepmother, Joanne, for never doubting that I *could* do this, and to my in-laws, Jim and Alexandra, for never doubting that I *would*;

Reverend Dr. Deborah Warren for her friendship and perspective;

my friend Alison Colbert, for some truly enjoyable collaborative projects, but more so, for helping me *believe* that juggling everything was possible; for helping me do it week, after week, after week; and, for making it *fun*;

my ultramarathoning sister, Kira, for the ongoing inspiration to run over the last 6 years, which has helped me retain my sanity;

my children, Zoe and Elliott, for making me proud to be a mother, and for rounding out my life;

and to my husband John, for taking so many leaps of faith with me (often blindfolded and over ditches), rolling through the inconveniences and the insanities, and for helping me make this happen by believing in me.

This work is dedicated to the memory of my mother, Ann Matukaitis, who juggled it all and then some, and who was always my #1 fan.

My graduate education was made possible through a Ruth L. Kirschstein National Research Service Award (NRSA) from the National Institute of Nursing Research, ("Substance Users, HIV Infection, and Adherence," F31NR008822), and through several graduate researcher positions under Dr. Mary Beth Happ (NINR, R01 NR07973; NICHHD, R01 HD043988; NINR, K24 NR010244).

1.0 INTRODUCTION

Previous research on alcohol use and HIV/AIDS has primarily addressed alcohol consumption within the context of risky sexual behavior and HIV transmission (Caetano & Hines, 1995; Ryan, Huggins, & Beatty, 1999; Stall, McKusick, Wiley, Coates, & Ostrow, 1986). However, in the last ten years, as treatment and survival for persons with HIV/AIDS (PWHIV) has dramatically improved, attention has slowly turned toward understanding the impact of alcohol use on antiretroviral (ART) medication adherence. Although approximately 40-55% of PWHIV acknowledge various degrees of alcohol use (Chander, Lau, & Moore, 2006; Galvan et al., 2002; Lucas, Gebo, Chaisson, & Moore, 2002; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003), understanding the influence of alcohol use on adherence continues to be limited (Chander, Himelhoch, & Moore, 2006). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has recently identified the need for increased research on improving medication adherence among HIV+ individuals who use and misuse alcohol, including the development of explanatory models that "increase understanding of the multidimensionality of the relationship between alcohol use and "abuse" and adherence to HIV therapeutic regimens. . ." (Bryant, 2006, p. 1492), i.e., models which include the variety of individual, social, and contextual factors affecting alcohol use and health behavior.

Suboptimal ART adherence contributes to decreased viral suppression and drug resistance, and subsequently, the potential for higher healthcare costs and the proliferation of resistant strains of HIV in the community. While attention to ART adherence among illicit drug users has appreciably increased in recent years, few ART adherence investigations have focused on the impact of alcohol use, in particular, on its impact independent from that of drug use. Studies exploring the relationship between alcohol and ART adherence report inconsistent findings, and often require careful evaluation in light of various methodological limitations, e.g., inconsistent or ambiguous definitions and measurement of "alcohol use" and "adherence," and the exclusive use of self–report data for assessment of adherence patterns (Chander, Himelhoch et al., 2006; Cook et al., 2001). Finally, a limited number of studies have heretofore attempted to elucidate the role of various psychological and environmental factors in the alcohol-adherence relationship such as self-efficacy, depressive symptoms, social support, and personality (Braithwaite et al., 2005; Parsons, Rosof, & Mustanski, 2007; Tucker et al., 2004), and only a few studies have described tailored adherence interventions aimed at PWHIV who drink (Parsons, Golub, Rosof, & Holder, 2007; Samet et al., 2005).

Important questions remain about how different patterns of alcohol consumption interfere with ART adherence, the mechanisms through which this interference might occur, and the effectiveness of ART adherence-enhancing interventions among PWHIV who consume alcohol. Given the prevalence of alcohol use, the significant personal and public health implications of suboptimal ART adherence, and the fact that alcohol use is a modifiable behavior, a more comprehensive understanding of the interplay between alcohol use, adherence, and various personal, behavioral, and environmental factors is warranted.

Within the framework of Social Cognitive Theory, the overall purpose of this secondary data analysis (SDA) was to further elucidate the impact of alcohol use on the ART adherence of PWHIV. The primary aims of the study were to: 1) characterize the sample; 2) determine if positive screening results on the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) provide additional prediction of ART dose adherence, day adherence, days under-dosing, days over-dosing and days with null dosing after controlling for various sociodemographic, substance use, and psychosocial variables; and 3) explore whether self-efficacy mediates the effects of depressive symptoms, social support, and conscientiousness on dose adherence, and to determine if any meditational relationships were moderated by alcohol screening status (AUDIT-C positive/negative). Secondary aims were to 1) explore whether self-efficacy mediates the effects of depressive symptoms, social support, and conscientiousness on the dose adherence of PWHIV with positive alcohol screening tests, and 2) evaluate selected psychometric properties of the AUDIT-C.

2.0 BACKGROUND

Medication-taking is an essential component of self-management in HIV/AIDS. Antiretroviral therapy (ART) is the combination of drugs designed to inhibit the proliferation of HIV, improve the patient's immunological status, and prolong life (Hogg, 1997; Palella, 1998). Medication *adherence* refers to the degree to which an individual follows or conforms to the prescribed therapeutic regimen. Although often referred to as "compliance," the less problematic term "adherence," is used here, with the recognition that "adherence" nonetheless retains many of the same conceptual and ethical limitations (Broyles, Colbert, & Erlen, 2005). Suboptimal adherence to ART regimens (generally understood to be <95%) (Paterson et al., 2000) contributes to viral resistance, poorer clinical outcomes for the individual, and the potential public health crisis of resistant strains of HIV (Bayer & Stryker, 1997; Lerner, 1998; Nieuwkerk et al., 2001; Plettenberg et al., 2001; Wainberg & Friedland, 1998).

Antiretroviral medication adherence is associated with multiple interwoven patient-, medication-, disease-, environment-, and system-related factors. Substance abuse is a common factor associated with ART nonadherence, though focused investigation on *alcohol* use and medication-taking practice in HIV/AIDS is relatively recent and limited compared to research examining the impact of *illicit drug use*. Reasons for this disparity may be related to the general social acceptability of alcohol use over illicit drug use, perceptions that alcohol use is the "lesser

of two evils" when compared to other substance use, or increased attention to drug use because of its more overt relationship to HIV transmission. Nonetheless, understanding the extent of alcohol use among persons with HIV/AIDS remains important because of its apparent roles in a variety of interwoven HIV-related processes and outcomes (Conigliaro, Justice, Gordon, & Bryant, 2006). Among HIV-infected individuals, alcohol use has been associated with decreased viral suppression and/or immune status (Chander, Lau, et al., 2006; Conigliaro, Gordon, McGinnis, Rabeneck, & Justice, 2003; Samet et al., 2007), decreased survival (Braithwaite et al., 2007), increased rates of comorbid medical illness (Justice et al., 2006), decreased neurocognitive function (Durvasula, Myers, Mason, & Hinkin, 2006), and potential medication interactions and toxicities (Department of Health and Human Services, 2008).

Importantly, alcohol may exert its effect on HIV-related processes and outcomes directly, or, more indirectly, i.e., through its impact on ART adherence. Alcohol use is generally associated with decreased ART adherence and a dose-response effect appears to exist where greater alcohol consumption is associated with greater likelihood of taking medications off-schedule or missing medication doses/days (Braithwaite et al., 2005; Chander, Lau et al., 2006; Samet, Horton, Meli, Freedberg, Palepu 2004; Tucker et al., 2003). The exact mechanisms through which this nonadherence occurs are heretofore unclear but presumably involve the interplay of numerous interrelated factors in addition to alcohol and medication-taking.

2.1 THEORETICAL FRAMEWORK

Social Cognitive Theory (SCT) guided the development of the parent study (PS) interventions and the selection of variables and analytic strategies for the current study. SCT is well-suited for understanding medication adherence in the context of chronic illness because it calls attention to the complex synergistic relationships between dimensions of the individual, the environment, and the behavior. More specifically, SCT asserts that behavior acquisition and maintenance are based on the idea of "reciprocal determinism," i.e., the bidirectional dynamic interplay between individual person factors (affective, cognitive, biological), environmental (social, physical) factors, and the behavior itself (Bandura, 1997). The primary causal processes in the acquisition and maintenance of a given behavior are driven by self-efficacy.

Formally defined as "beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments" (Bandura, 1997, p. 3), self-efficacy is commonly understood as confidence in one's own ability to perform a specific behavior or task, i.e., to influence or control a given behavioral outcome. Self-efficacy beliefs influence one's choices, effort expenditure, perseverance/resilience, thoughts, and emotional reactions (Bandura, 1997). Additionally, behavior change and maintenance are functions of the individual's expectations about his/her ability to perform a behavior (*efficacy expectations)*, as well as of the expectations that the behavior will in fact lead to the desired outcome *(outcome expectations)* (Bandura, 1997). Efficacy expectations mediate the process between the person and the enactment of the behavior, and outcome expectations do the same for the process between behavior enactment and the outcome. Importantly, in contrast to more global constructs such as self-esteem, self-efficacy is behavior-specific and context-specific (Bandura, 1997); one may possess considerable self-

efficacy for behavior A, but not for behavior B, or one may possess high self-efficacy for behavior A in context Y but not in context Z.

Self-efficacy can be acquired through *mastery experiences, vicarious experience, social persuasion, and somatic/emotional states* (Bandura, 1997). Mastery experiences are the most effective source of creating a sense of self-efficacy; an individual's prior successes with a specific behavior lead to a belief in one's capability to execute it in the future. Vicarious experience, observing the social modeling of others, raises one's beliefs in his/her own abilities, so long as the "others" possess perceived similarity to the individual. Social persuasion, or conveying positive appraisal, can also help people increase their self-efficacy, though its effects are the weakest of the four sources. Finally, one's perceptions of physiologic and emotional cues can enhance or hinder self-efficacy as one transcends or succumbs to various physical and emotional responses to the activity (Bandura, 1997) .

With its attention to sociostructural and personal determinants of behavior and its focus on self-regulation, SCT fully considers the multiple spheres of influence on medication-taking, speaks to the self-regulatory and adaptive management skills needed by individuals with chronic disease, and fits well with the undulating nature and persistent demands of chronic illness itself. In Specific Aim #2, SCT guided the current study's broad inclusion of confounders and covariates in the multiple linear regression models designed to predict adherence. These confounders and covariates represent the three previously mentioned interactive realms of person factors (affective, cognitive, biological), environmental (social, physical) factors, and behavior. This modeling of adherence also recognizes the numerous intersecting influences on medication-taking. In Specific Aim #3, the current study evaluated the effectiveness of the PS interventions which were rooted in SCT and which aimed to improve ART adherence through self-efficacy

enhancement and skill-building in habit development, self-monitoring, and problem-solving. The current study also sought to determine if the intervention effectiveness varied (i.e., was moderated) by person factors such as alcohol use. Finally, in Secondary Aim #1, the potential mediational role of self-efficacy on the process(es) between the person/environment and the behavior was evaluated, as was the potential for moderation of these relationships by alcohol use.

2.2 ALCOHOL USE AMONG PERSONS WITH HIV/AIDS

Estimates of the prevalence and degree of alcohol use among persons with HIV/AIDS (PWHIV) vary depending on the sample and assessment strategy used. However, in general, approximately 40-55% of persons with HIV/AIDS endorse alcohol use of some kind, with 10-20% of those individuals consuming alcohol at hazardous or risky levels (Arnsten et al., 2002; Braithwaite et al., 2005; Chander, Lau et al., 2006; Conigliaro et al., 2006; Cook et al., 2001; Galvan et al., 2002; Halkitis, Parsons, Wolitski, & Remien, 2003; Lucas et al., 2002; Samet, Horton, et al., 2004; Tucker et al., 2003; Waldrop-Valverde et al., 2006) (for additional references, see Appendix A). In a large study based on data from the HIV Cost and Services Utilization Study (HCSUS), Galvan et al. (2002) noted that 53% of the participants acknowledged drinking in the past month; of those who drank, 15% were heavy drinkers ($\geq$5 drinks on $\geq$4 days/week in the previous 4 weeks). Among studies using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) categorization of alcohol use, i.e., where "hazardous use" is defined as >7 drinks/week or >3 drinks per occasion for women and as >14 drinks/week or >4 drinks per occasion for men, and where "moderate use" is defined as any alcohol use at less than these levels (National

Institute on Alcohol Abuse and Alcoholism, 2005), rates of moderate use range from 24-35%, and rates of hazardous use range from 11-16% (Chander, Lau et al., 2006; Samet, Horton, et al., 2004). In one study of over 800 HIV-infected veterans, 20% were classified as hazardous drinkers (i.e., a score of $\geq$8 on the Alcohol Use Disorders Identification Test) and 33% as binge drinkers. Additionally, 27% had at least one International Statistical Classification of Diseases (ICD-9) alcohol-related diagnosis in the previous 5 years (Conigliaro et al., 2003). Cook et al. (2001) classified 19% of its HIV-infected outpatient sample as "problem drinkers" (i.e., $\geq$1 of the following consumption profiles—binge, heavy, or hazardous drinking) and 33% as mild-moderate drinkers.

Determining the rate and impact of alcohol consumption among PWHIV is complicated by several factors. Given the general tendency to under-report alcohol use, and the fact that some large-scale studies did not specify for participants the amount of alcohol constituting "a drink" (Galvan et al., 2002), general alcohol consumption by PWHIV may, in fact, be higher. Of note, other studies of HIV-infected persons have reported rates of alcohol use as high as 67-80% (Chesney et al., 2000; Justice et al., 2006; Lefevre et al., 1995), with rates of "alcoholism" (as defined by Michigan Alcoholism Screening Test scores $\geq$5) exceeding 40% (Lefevre et al., 1995). Finally, concomitant drug use/abuse is common among HIV-infected persons who consume alcohol (Chander, Himelhoch et al., 2006; Galvan, Burnam, & Bing, 2003). The realities of polysubstance use make determining the independent effects of alcohol on ART adherence challenging; however, disentangling these effects remains important given the wide spectrum of alcohol use and its ubiquitousness within Western culture.

2.3 GENERAL ASSOCIATIONS BETWEEN ALCOHOL USE AND ART ADHERENCE

From investigations focused on alcohol users to broad studies of predictors/correlates of ART adherence, alcohol use is generally, though not entirely consistently, associated with poorer ART adherence (see Appendix A for overview). In the earliest of studies specifically examining alcohol use and ART adherence, both hazardous and heavy alcohol use were significantly associated with taking ART medications off-schedule in the previous week, and problem drinkers (binge, heavy, hazardous) were significantly more likely than non-problem drinkers to report drinking and/or using drugs as a reason for missing ART doses in the previous 24 hours (Cook et al., 2001). Likewise, in a cohort of persons with lifetime alcohol problems, alcohol consumption emerged as the most significant predictor ($p < .0001$) of 3-day self-reported dose adherence. At-risk and moderate drinkers were significantly less likely than non-drinkers to report 100% dose adherence for the previous 3-day period (Samet, Horton, et al., 2004). An additional investigation using the same cohort similarly reported that the use of alcohol and/or drugs in the previous 30 days was negatively associated with $\geq$ 95% adherence (Palepu, Horton, Tibbetts, Meli, & Samet, 2004). In a study of men who have sex with men, those who drank several times per week had significantly more missed medication days than infrequent drinkers and non-drinkers (Halkitis et al., 2003).

Like their quantitative counterparts, qualitative investigations of adherence generally support the notion that alcohol interferes with ART self-administration. Persons with HIV/AIDS have reported that immediate substance cravings often take precedence over ART medication-taking (Laws, Wilson, Bowser, & Kerr, 2000; Malcolm, Ng, Rosen, & Stone, 2003; Remien et

al., 2003); that they often avoid taking ART because of concerns that the medication will be rendered ineffective by alcohol or drugs (Malcolm et al., 2003; Pach, Cerbone, & Gerstein, 2003; Sankar, Wunderlich, Neufeld, & Luborsky, 2007), and that "drinking and drugging" is a significant barrier to taking ART (Powell-Cope, White, Henkelman, & Turner, 2003).

On the other hand, other investigators have found no relationship between ART adherence and a variety of alcohol use patterns. For example, in two studies of individuals enrolled in methadone maintenance, frequent or binge alcohol use was not associated with median ART adherence rates (Arnsten et al., 2002; Berg et al., 2004). In one study, baseline alcohol consumption of >1 unit/day of alcohol was not significantly associated with adherence (Spire et al., 2002), while in another, neither was consuming >14 drinks/week (Kleeberger et al., 2001). Studies using electronic event monitors, multiple measures of adherence, and comprehensive assessments of substance use (e.g., the Substance Use module of the SCID for DSM-IV) have also reported no significant relationship between alcohol use and ART adherence (Halkitis, Kutnick, & Slater, 2005; Hinkin et al., 2004; Paterson et al., 2000; Waldrop-Valverde et al., 2006). Again, these somewhat contradictory results are likely due to the substantial differences in how adherence and alcohol use are defined and measured across studies. However, among nonintervention studies demonstrating a significant relationship between alcohol use and ART adherence, several themes emerge related to dose and time.

2.4 DOSE-RESPONSE AND TEMPORAL ASSOCIATIONS

First, a general dose-response relationship appears to exist, where increasing levels of alcohol consumption are associated with increasing odds of nonadherence. For example, Tucker and colleagues reported that the percentage of adherent persons consistently decreased as alcohol consumption level increased, i.e., 52% of nondrinkers were adherent, compared to 43% of nonheavy drinkers, 39% of heavy drinkers, and 31% of frequent heavy drinkers. Additionally, in multivariate analysis, all three levels of alcohol consumption significantly increased the odds of nonadherence (Tucker et al., 2003). Similarly, among veterans with fluctuating alcohol consumption patterns (i.e., combination binge/nonbinge), missed medication doses were more likely to occur on binge days, followed by nonbinge days, and non-drinking days. Additionally, in multivariate analysis (controlling for drug use, age, education, and depression), compared to HIV+ *non*-drinkers, HIV+ nonbinge and binge drinkers had significantly greater odds of nonadherence (Braithwaite et al., 2005). Even more recently, Chander, Lau, and Moore (2006) reported that both hazardous and moderate alcohol use were associated with decreased odds of self-reported 2-week ART adherence compared to no use. Finally, further dimensionalizing alcohol use, Parsons, Rosof, & Mustanski (2007) reported that in a sample of persons with alcohol problems (score $\geq$8 on the Alcohol Use Disorders Identification Test [AUDIT]) the number of drinks consumed significantly predicted adherence, but negative consequences of alcohol use or one's total AUDIT score did not.

Second, a temporal relationship between alcohol use and medication adherence has also been reported, further suggesting a degree of causality between alcohol use and ART nonadherence. Among HIV-infected veterans, alcohol consumption on a given day was

significantly associated with decreased medication (ART and non-HIV) adherence on that day as well as the two days immediately thereafter. This pattern was consistent for nonbinge drinkers and binge drinkers, and remained significant even after removing individuals who endorsed concomitant illicit drug use from the analysis (Braithwaite et al., 2005).

2.5 RATES OF ADHERENCE/NONADHERENCE AMONG PWHIV WHO USE ALCOHOL

Despite the apparent effects of alcohol on medication-taking, rates of ART adherence among PWHIV who use alcohol appear to mirror estimates of ART adherence among PWHIV in general. In studies specifically examining the relationship between alcohol use and ART adherence, and among those intentionally using samples of HIV-infected persons with alcohol problems, overall or baseline rates of ART nonadherence range from approximately 15-55% (Braithwaite et al., 2005; Cook et al., 2001; Parsons, Rosof et al., 2007; Samet, Horton, et al., 2004). In one study which classified individuals as hazardous, heavy, or binge drinkers based on the AUDIT and two quantity/frequency questions, 30% of participants reported not taking their ART medication(s) as scheduled in the previous week, and 14% acknowledged an ART dose in the previous 24 hours (Cook et al., 2001). In a sample from the Veterans Aging Cohort Study (VACS) where the Time Line Follow Back (TLFB) method was used to assess drinking over the previous 30 days, 44% of participants acknowledged missing or taking late (>2 hours) doses (Braithwaite et al., 2005). Rates of nonadherence also vary considerably

(~30-60%) in studies which examined the impact of alcohol use on adherence within more heterogenous samples (Haubrich et al., 1999; Spire et al., 2002; Waldrop-Valverde et al., 2006).

In general, however, rates of ART adherence among PWHIV who use alcohol are somewhat difficult to ascertain due to 1) wide variation in definitions and operationalization of both adherence and alcohol use, 2) the common practices of assessing alcohol and drug use simultaneously, treating alcohol and drug users as a single population (e.g., "substance users"), or combining alcohol and drug use into a single variable (e.g., "alcohol or drug dependence"), and 3) the simple underreporting of such numbers. Furthermore, these rates of adherence/nonadherence are not always delineated by factors such as alcohol consumption level, or by demographic factors such as race/ethnicity and gender.

2.6 GENDER DIFFERENCES

An understanding of alcohol's impact on adherence among women is particularly limited, and may in fact be underestimated. Women consistently constitute less than 50% of the sample in existing studies, and some studies have used instrument cut-off scores or alcohol use classifications which fail to accurately capture or categorize female drinkers. For example, several studies used a general cutoff score of 8 for the AUDIT (Lucas et al., 2002; Parsons, Golub et al., 2007; Parsons, Rosof et al., 2007), which reduces sensitivity for detecting problematic drinking in women; subsequently, these studies may have only captured the most severe female drinkers. While the low percentage of women enrolled in ART adherence studies may in part simply reflect the epidemiology of HIV/AIDS, their under representation limits the

generalizability of findings with respect to alcohol use and adherence; several studies suggest that gender differences are present (Berg et al., 2004; Howard et al., 2002; Lazo et al., 2007).

In a multicenter study of HIV+ women where 85% of the sample belonged to racial/ethnic minority groups, and almost one-fourth were enrolled in methadone maintenance, significantly poorer adherence (via EEM) was found among women with alcohol use greater than or equal to once/week (mean adherence rate 46% vs. 56%). Alcohol use once/week or more remained significantly associated with adherence in multivariate analysis (Howard et al., 2002). Although the operationalization of alcohol use employed in the study by Howard and colleagues is atypical and potentially reflects a wide variety of frequency and consumption patterns, their results raise questions about the harmful impact of even small or relatively infrequent degrees of alcohol use, particularly for women, women of color, and/or women with polysubstance use problems. Using a similar sample and EEM, another study exploring gender differences in ART adherence found no significant differences in adherence between those with and without "problem alcohol use" ($\geq$5 drinks/occasion *or* drinking "several days per week" or "every day"); however, a significant interaction between gender and alcohol use was detected where women with "problem alcohol use" were significantly less adherent than men meeting this criterion (Berg et al., 2004). Finally, in a large-scale analysis of data from the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS), Lazo and colleagues (2007) recently reported that binge drinking, moderate to heavy alcohol consumption, and low alcohol consumption were all independent predictors of decreasing ART adherence, but only among women. Similarly, binge drinking and low alcohol consumption emerged as independent inverse predictors of increasing adherence in women only; however, the use of two or more illicit drugs was an inverse predictor of increasing adherence for both genders (Lazo et al., 2007).

Collectively, these studies generate new questions about the web of intersections between sociodemographic characteristics, alcohol, adherence, and other psychosocial and environmental factors.

2.7 MECHANISMS AND MEDIATORS

Although the previously described dose-response and temporal effects of alcohol on ART adherence lend support to the notion of some degree of causality between alcohol use and nonadherence, the underlying mechanisms for this relationship remain unclear. Additional gaps exist with respect to the larger constellation of interrelated variables affecting alcohol and adherence. These gaps include various person-level and environmental factors suggested to be important by Social Cognitive Theory, namely, self-efficacy, depressive symptoms, social support, and personality characteristics.

2.7.1 Self-efficacy

Self-efficacy is an integral component of major theoretical frameworks addressing health behavior change, including SCT and the Health Belief Model. Self-efficacy for taking ART is a consistent predictor of ART adherence (Ammassari et al., 2002). In one study of correlates to HAART adherence, each reduction in standard deviation unit of self-efficacy was associated with more than twice greater odds of ART nonadherence (Catz, Kelly, Bogart, Benotsch, McAuliffe, 2000). In another study of men who have sex with men, low self-efficacy and high

avoidance coping were both related to poorer adherence, and individuals with >95% adherence had significantly higher self-efficacy levels than those with adherence ranging from 80-90% and <80% (Halkitis et al., 2005). Additionally, a mediational role for self-efficacy in ART adherence has been demonstrated whereby self-efficacy mediates the role of other factors such as social support, depressive symptoms, and patient-provider relationships (Cha, Erlen, Kim, Sereika, & Caruthers, 2007; Johnson et al., 2006; Luszczynska, Sarkar, & Knoll, 2007; Simoni, Frick, & Huang, 2006). In contrast, one study of ART adherence predictors among individuals with alcohol problems reported that *adherence* mediated the relationship between self-efficacy and HIV viral load (Parsons, Rosof, & Mustanski, 2008). However, the precise nature of self-efficacy's relationship to other psychosocial variables and outcomes in PWHIV remains unclear, particularly for PWHIV who consume alcohol. Alcohol and other substance use may reduce self-efficacy for self-care behaviors such as ART adherence.

2.7.2 Depressive symptoms

Depression has also been associated with ART adherence, though less consistently (Ammassari, et al., 2002; Berger-Greenstein et al., 2007; Chander, Himelhoch et al., 2006). In a large study based on HCSUS data, individuals with depression had greater odds of nonadherence (Tucker et al., 2003), but in other studies, significant relationships between depression and adherence were not sustained in multivariate analysis (Catz et al., 2000). Antidepressant treatment appears to improve ART adherence; however, these findings are not conclusive (Chander, Himelhoch et al., 2006). The intersection of alcohol, depression, and ART adherence has also been a recent focus of investigation. In one study of adherence among PWHIV with alcohol problems, no significant

differences in depressive symptoms were detected across drinking groups (abstinent, moderate, at-risk), though depressive symptom scores did emerge as a significant factor associated with decreased odds of having 100% adherence in the previous three days (Samet, Horton, et al., 2004). The nature of these relationships remains imprecisely defined, particularly in light of the established interrelationships between self-efficacy and depression, and depression and problematic alcohol use.

2.7.3 Social support

Social support is consistently associated with ART adherence (Ammassari et al., 2002; Catz et al., 2000; Murphy, Marelich, Hoffman, & Steers, 2004; Vyavaharkar et al., 2007), and its presence in mediational models has been noted above. Importantly, numerous path analyses and other modeling studies have revealed the parallel and inverse relationships between social support and negative affect/depressive symptoms, and their subsequent impact on coping, self-efficacy, and in turn, on ART adherence (Simoni et al., 2006; Vyavaharkar et al., 2007; Weaver et al., 2005). These complex interrelationships have not been specifically examined in the context of alcohol use among PWHIV. Nonetheless, understanding the linkages between these variables is essential for guiding the development of adherence interventions for individuals who use alcohol, a subgroup of PWHIV which has only recently begun to receive special attention.

2.7.4 Personality characteristics

Individual differences in personality may contribute to differences in medication adherence because of their impact on processes such as motivation, coping, problem-solving, and self-regulation. The Five Factor model of personality provides a popular conceptualization of personality structure where five overarching factors (Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism) represent the broadest dimensions of personality and summarize more specific characteristics/traits. For example, the dimension of conscientiousness represents personality traits such as competence, efficiency, organization, self-discipline, and deliberation (Costa & McCrae, 1992) Although the five factors can be considered "basic tendencies" which drive the development of "characteristic adaptations," responses, or attitudes in the individual, five factor models are best considered "grand theories" of human functioning (Costa & McCrae, 1999).

Relationships between five-factor personality traits and medication adherence in chronic illness have previously been reported. High conscientiousness has been associated with adherence to cholesterol-lowering medications (Stilley, Sereika, Muldoon, Ryan, & Dunbar-Jacob, 2004), and among renal patients, with adherence to phosphate binders (Christensen & Smith, 1995). Low levels of another trait, Agreeableness, have been associated with poor adherence to medication regimens for inflammatory bowel disease (Ediger et al., 2007).

Examination of personality and medication adherence among PWHIV, however, is relatively new (Cruess, Minor, Antoni, & Millon, 2007; Johnson & Neilands, 2007; Penedo et al., 2003). Johnson & Neilands (2007) reported that greater Neuroticism scores on the NEO-FFI were associated with greater frequency and severity of ART side effects. They suggest that this

finding is important with respect to adherence insofar as side effects play a major role in altered patterns of medication-taking (Johnson & Neilands, 2007). In a study exploring variables associated with quality of life in HIV/AIDS, Penedo et al (2003) found no direct relationship between personality traits and ART adherence. The authors however, specifically acknowledge that the lack of expected findings in this realm may have been attributable to sampling and measurement decisions, i.e., the exclusion of persons with alcohol/drug use, the use of a self-report measure for adherence (as opposed to EEM), and the limited window of adherence examined (previous four days) (Penedo et al., 2003).

Another study of PWHIV investigating personality and ART adherence used a measure which included an assessment of coping styles, described as "similar to personality characteristics. . .the pervasive ways in which patients habitually approach and deal with their life experiences" (Cruess et al., 2007, p. 281). These authors reported a variety of coping styles to be significantly associated with overall ART adherence and/or specific medication-taking behaviors. For example, the Dejected coping style (persistently disheartened, easily disposed to give up) was significantly associated with < 95% adherence, taking more medications than prescribed, and skipping medications. Similarly, the Oppositional (unpredictable, difficult) and Nonconforming (unconventional arbitrary, impulsive) styles were also significantly associated with skipping medications. Of note, individuals with alcohol and drug use disorders were excluded from the sample (determined by the Structured Clinical Interview for DSM Disorders [SCID]), the mean number of alcoholic drinks consumed in the previous 3 months was 13.92 (*SD* = 36.19), and multiple analyses controlled for alcohol and/or drug use (Cruess et al., 2007).

In one of its exploratory aims, the secondary data analysis (SDA) pursued this relatively new avenue of inquiry (i.e., personality characteristics and ART adherence), and addressed some

of the limitations in the earlier studies by including individuals who use alcohol and drugs, and by using EEM for longitudinal adherence assessment.

2.8 ART ADHERENCE INTERVENTIONS FOR ALCOHOL USERS

Two randomized controlled trials (RCTs) have specifically aimed to improve ART adherence, reduce alcohol consumption, and improve clinical outcomes in PWHIV who have alcohol problems. Important differences, however, exist not only in terms of study results, but with respect to theoretical underpinnings; study design (i.e., selection of comparison group); intervention design, duration, and intensity; and alcohol and adherence dimensionalization and assessment (see Appendix B).

Using a sample of "hazardous drinkers," Parsons, Golub, et al. (2007) compared a theoretically-driven ART adherence intervention with an ART/alcohol *education condition*. The adherence intervention consisted of motivational interviewing for alcohol reduction, as well as tailored self-assessment, monitoring, and skills-building, while the education condition used a didactic approach (discussion, videotapes) on ART, alcohol, and adherence. Significant improvements in dose and day adherence in both groups from baseline to three months were reported, with the intervention group reporting significantly greater improvement*s* in both compared to the education group. Adherence improvements were not sustained at the three month time point, but alcohol consumption significantly decreased in both groups at three months and six months (Parsons, Golub et al., 2007).

This study possessed several characteristics previously noted to be associated with intervention efficacy, namely the study's low baseline percentage of adherent individuals and intervention design. One meta-analysis of ART adherence interventions reported that intervention studies targeting persons with low adherence at baseline showed larger effect sizes than those that did not enroll in this manner (Amico, Harman, & Johnson, 2006). While the study by Parsons et al. did not target low adherers during enrollment, baseline adherence was 38% for the sample. Another meta analysis reported that interventions incorporating "interactive discussion of cognitions, motivations, and expectations regarding adherence" also showed greater effect sizes than those that did not (Simoni, Pearson, Pantalone, Marks, & Crepaz, 2006, p. S31). Due to its complexity, however, this intervention may be challenging to replicate in the clinical setting; adjusting the intervention may be necessary.

Samet et al (2005) compared the effect of an adherence-enhancing intervention with *usual care* in a sample of persons with current or lifetime alcohol abuse/dependence and found no significant differences in ART adherence, alcohol consumption, CD4 count, or viral load. The four-session study intervention was clinically feasible in terms of duration and intensity, and combined information needs (ART) and readiness to change (substance use), with practical, life-relevant dimensions, elements previously noted to be important and effective components of ART adherence interventions (Rueda et al., 2007). Nevertheless, the lack of significant findings is potentially attributable to a lack of statistical power, incomplete intervention administration for ~25% of the sample, and a large percentage of adherent individuals at baseline (Samet et al., 2005). Furthermore, broad inclusion criteria ("current or lifetime alcohol abuse or dependence") may have also influenced the results. Information about severity of drinking, current alcohol consumption patterns, and the distribution of alcohol use categories was not reported, and limited

information about the theoretical underpinnings and specific content of the intervention leave questions about the role of intervention design in the study's lack of significant findings. Given these various limitations, the authors' conclusions about the potential need for directly observed therapy (DOT) in this population are potentially premature.

The use of a "directly observed" or "directly administered" intervention for improving ART adherence among alcohol and drug users has been examined elsewhere as well, though primarily among injection drug users or individuals on methadone maintenance (Altice, Maru, Bruce, Springer, & Friedland, 2007; Chander, Himelhoch et al., 2006; Conway et al., 2004; Lucas et al., 2007). Macalino et al. (2007) conducted a randomized controlled trial of antiretroviral DOT for substance users where 17% of the sample misused alcohol exclusively, and reported that individuals on DOT were more likely to achieve viral suppression than individuals receiving standard care (Macalino et al., 2007). In another DOT study where 36% of the injection drug-using sample consisted of problematic drinkers, adherence was significantly higher for supervised versus unsupervised doses (Altice et al., 2004). These studies suggest that DOT may be an effective adherence promotion strategy in certain conditions and circumstances; however, when samples are comprised of active drug and alcohol users, differentiating the effects of DOT for each subgroup is somewhat compromised. Additional research is needed to uncover the conditions, circumstances, and patient populations best suited for this type of adherence intervention.

2.9 ALCOHOL SCREENING IN PERSONS WITH HIV/AIDS

In order to select the most appropriate, patient-centered care and individualized adherence enhancement interventions for PWHIV, HIV/AIDS care providers need accurate and efficient assessment of alcohol risk behavior (Conigliaro et al., 2003; Cook et al., 2001; Petry 1999; Samet, Phillips, Horton, Traphagen, & Freedberg, 2004). One alcohol screening instrument with the advantages of brevity and sensitivity is the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). The AUDIT-C is an alcohol screening tool based on the first three (consumption-related) items from the full 10-item Alcohol Use Disorders Identification Test (AUDIT), a screening questionnaire developed by the World Health Organization and validated internationally for the detection of "hazardous and harmful drinking patterns" (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). The sensitivity and specificity of the AUDIT-C for the detection of hazardous drinking and active alcohol abuse/dependence parallels or exceeds that of comparable instruments used in clinical and research settings (e.g., standard quantity/frequency questions, CAGE, full AUDIT) (Bradley, et al., 2003; Bradley et al., 2007; Bush et al., 1998; Frank, et al., 2008; Gordon, et al., 2001). Additionally, the third question on the AUDIT-C which addresses episodic heavy/binge drinking (AUDIT-3) generally demonstrates slightly lower, but highly adequate sensitivities when used alone as a single alcohol screening question (Bradley, et al., 2003; Bradley et al., 2007; Gordon, et al., 2001). Because of its psychometric properties and the ease of its administration and scoring, the AUDIT-C is one of the alcohol screening tools recommended by the NIAAA; a single screening question similar to the AUDIT-3 is also recommended (NIAAA, 2005).

Interestingly, scores on the AUDIT-C and the AUDIT-3 have also been directly associated with the incidence of other health-related outcomes such as risk of hospitalizations for gastrointestinal conditions such as liver disease, upper GI bleeds, and pancreatitis (Au, Kivlahan, Bryson, Blough, & Bradley, 2007) and general 5-year mortality rates (Bradley, Maynard, Kivlahan, McDonell, & Fihn, 2001). Given these findings, a reasonable question is whether the AUDIT-C and AUDIT-3 might also predict health behaviors such as ART adherence. While various versions of the AUDIT have been used by adherence researchers for assessing alcohol use, no published study has heretofore considered the potential for this type of dual purpose.

In order to proceed with such multi-function use of the AUDIT-C, additional psychometric evaluation of the instrument is also needed. While the full AUDIT (from which the AUDIT-C is derived) was validated on primary care patients in six different countries and appears to perform relatively well across gender and race/ethnicity (Babor, et al., 2001; Reinert & Allen, 2007), limited psychometric data is available on the AUDIT-C as a stand-alone instrument, particularly with the inclusion of gender/race evaluations, and no psychometric evaluations to date have used samples of PWHIV. Limited research has demonstrated that the sensitivity and specificity of the AUDIT-C also varies across gender and race, however, only the use of gender-specific cut-points has been explicitly recommended (Bradley et al., 2003; Bradley et al., 2007; Dawson, Grant, Stinson, & Zhou, 2005; Frank et al., 2008). Nonetheless, wide variation in alcohol consumption patterns, alcohol-related social norms, and alcohol-related biopsychosocial problems both across and within racial/ethnic groups (Caetano, Clark, Tam, 1998) and across gender (Collins & McNair, 2002; Green, Perrin, & Polen, 2004; Wilsnack & Wilsnack, 2002) suggests that further examination of the reliability, validity, and factor structure of the AUDIT-C by gender/racial subgroups is warranted.

2.10 SIGNIFICANCE

This study answered the NIAAA call for elucidating and explicating the impact of alcohol on ART adherence by 1) exploring the baseline and post-intervention differences in ART adherence across alcohol screening status, i.e., AUDIT-C positive/negative, AUDIT-3 positive/negative; 2) explicating some of the avenues through which a variety of person-level and environmental factors affect optimal medication-taking among PWHIV who screen positive on alcohol screening tests; and 3) expanding knowledge about the accuracy and validity of alcohol screening instruments in PWHIV and across gender and race.

This study had numerous strengths. The use of the AUDIT-C to identify potential problem drinkers was clinically relevant, feasible, and recommended, thus increasing the translatability of the research for HIV care providers partnering with patients for optimal, individualized medication management. If positive screens on the AUDIT-C are predictive of ART adherence, the implementation of a systematic alcohol screening program using the AUDIT-C could improve the detection of both risk behaviors; in particular, by reminding clinicians to be alert to the greater risk of suboptimal adherence in those who screen positive for at-risk drinking. Finally, this study's use of EEM data provided accurate measurement and additional dimensionalization of medication adherence behavior. EEM is considered to be the near "gold standard" for adherence assessment, not only in terms of its reliability, but also in its ability to reveal various adherence patterns as opposed to simply identifying whether or not one is "adherent" (Sereika & Dunbar-Jacob, 2001).

Additionally, while extant studies demonstrate what appears to be a dose-response relationship between alcohol use and ART nonadherence, the processes through which this

occurs have remained unclear, thus limiting adherence intervention design and testing for persons who drink alcohol. Numerous questions remain about the optimal ways to address ART adherence in the context of alcohol use. Should ART adherence interventions simultaneously aim to reduce alcohol consumption across all levels of alcohol intake? If so, what is the best way to concurrently address adherence and drinking behavior? Results of this study have the potential to guide the development of personalized adherence enhancement interventions which integrate established adherence-improvement strategies with individual factors such as alcohol consumption level, mood, personality characteristics, self-efficacy, gender, and existing patterns of medication-taking. Results may provide further empirical evidence for the expansion of clinical guidelines about the general use of alcohol among PWHIV.

Finally, widespread screening for alcohol problems in clinical practice rests on the reliability and validity of alcohol screening instruments across subpopulations of patients. The results of this study's psychometric evaluation of the AUDIT-C speak to the appropriateness of its use in PWHIV, in women, and in racial/ethnic minorities.

3.0 RESEARCH DESIGN AND METHODS

3.1 SECONDARY DATA ANALYSIS

In order to address the aforementioned primary and exploratory aims, a secondary data analysis (SDA) was conducted using existing data from the study "Improving Adherence to Antiretroviral Therapy," R01NR04749—the "parent study" (PS). Secondary data analysis was an appropriate choice for this study insofar as the SDA and PS shared the same conceptual framework, an understanding of the variables of interest, and common co-investigators/consultants who have a longstanding history of professional collaboration. Additionally, SDA reduces participant burden; helps address recruitment and retention challenges associated with ill and/or substance-using populations; and reduces overall research costs (Ashery, 1992; Nicoll, 1999; Pollack, 1999; Schroeder, 2001).

3.2 PARENT STUDY OVERVIEW

Based on Social Cognitive and Self-Efficacy Theories (Bandura, 1986, 1997), the PS tested a cognitive behavioral ART adherence intervention over time. The study also examined the impact of adherence on clinical outcomes and quality of life, and the impact of self-efficacy on

adherence. Parent study participants were required to be ≥ 18 years old, on combination ART therapy, English-speaking, free from significant cognitive impairment, and community-dwelling with telephone access. Additionally, individuals were excluded from participation if they were living with another individual already enrolled in the study, had upper extremity or visual impairments which precluded self-administration of medication, or if they had hearing difficulties without adaptive telephone equipment for delivery of the telephone intervention. Participants were recruited from multiple sites (a university-based clinic, community and veterans' hospitals, and comprehensive care centers) in southwestern PA and northeastern OH**.**

3.2.1 Parent Study Design

The PS was a randomized controlled trial involving a three-arm design where participants were randomized to a structured adherence intervention condition, individualized adherence intervention condition, or usual care (control) condition using permuted blocks within strata (gender, race, CD4 count, viral load). Additionally, individuals in the two intervention groups were further randomized to receive three "booster" sessions of the intervention after the maintenance phase of the intervention.

In order to track medication-taking behaviors, participants were given an electronic event monitor (EEM) and a medication bottle and were instructed in the use and purpose of the EEM. For a one month induction period, PS participants used the EEM for a randomly selected ART medication (the monitored drug). Data from the last two weeks of this induction period were considered the baseline adherence assessment and were used to determine PS participants' general adherence status. Individuals with perfect adherence at baseline (i.e., "100% adherers")

were extracted for separate analysis by the PS as they were presumed to be unable to "improve" their ART adherence any further through the intervention being tested. The remaining participants with less than 100% adherence at baseline were then randomized to the three aforementioned conditions, and continued to use EEMs for adherence monitoring of the designated drug.

Based on Social Cognitive Theory, the 12-week *structured* adherence intervention addressed HIV/AIDS medication regimens, medication-taking barriers, side effects, and social support and was comprised of skill-building in habit development, self-monitoring, problem-solving, self-reflection, and reinforcement strategies. At the beginning of each session, the weekly concept was introduced by the interventionist, with a mutually agreed-upon aspect for application to the individual's own medication management; this allowed for differences in personal situations, lifestyles, and educational backgrounds. Nine sessions involved homework activities. Sessions were delivered weekly by telephone, followed a pre-determined format, and lasted approximately 15-30 minutes. For consistency, the same interventionist delivered all 12 sessions for each participant, and all sessions were delivered in the same order for all participants.

The inclusion of an *individualized* adherence intervention was based on exit interviews from an earlier phase of the PS. Participant responses indicated that some individuals found the content in the structured intervention sessions to be repetitive or no longer relevant to their lives after a certain point in time (e.g., participants had already addressed side effects issues related to their medications or had already developed effective habit strategies for medication-taking). Additionally, participants desired feedback about their adherence. Rooted in the principle of respect for autonomy, the individualized intervention was intended to address the

aforementioned issues, and was designed to be patient-specific and patient-driven. It contained the following elements: a needs assessment, content matching key characteristics/needs of the individual, a decision process for matching the intervention message to the individual's key characteristics, a specific means for delivering the intervention, and personalized feedback (Ryan & Lauver, 2002). Participants were contacted weekly for 12 weeks, and sessions averaged 20-30 minutes in duration. Broad discussion topics in the intervention included involvement in healthcare decision-making, adherence, disclosure of HIV status resources, care giving responsibilities, and knowledge of HIV and ART. Consistent with SCT, the discussions promoted skill-building in problem-solving, self-monitoring, self-reflection, reinforcement, and modeling. As with the structured intervention, the same interventionist delivered all 12 sessions for each participant.

Across sites, the usual care condition included physical examination; laboratory tests; medication teaching at each visit with a physician, a registered nurse, and/or pharmacist; adherence instruction; attention to drugs/dosing, and side effects; mental health and social services, general HIV education, and follow-up/referrals. The availability of these components of usual care was generally consistent across sites, with the exception of social services (5 out of 7 sites) and medication teaching by a pharmacist (available at 2 out of 7 sites). Of note, certain sites also had special programs (e.g., for women, or for family members).

3.3 SDA SAMPLING

For the SDA, no sampling exclusions were made based on race, gender, ethnicity, or sexual orientation, however, only randomized participants were included i.e., individuals deemed "100% adherers" were omitted from the current analysis (n=8), as were individuals who were removed from medications by their physicians during the induction phase (n=2) and individuals who did not return the EEM cap at the end of the induction phase (n=2). Because missing or inconsistent responses on AUDIT items 1-3 at baseline would impede categorization of individuals as AUDIT-C positive/negative and/or AUDIT-3 positive/negative by requiring incompletely justified interpretations about their response intentions, PS participants with completely missing (n=6) or inconsistent (n=18) AUDIT data on these items at baseline were removed from the sample prior to analysis. Inconsistent responses included, for example, a response of "never" to AUDIT question 1 ("How often do you have a drink containing alcohol?") and the simultaneous selection of a quantity greater than zero in response to AUDIT question 2 ("How many drinks containing alcohol do you have on a typical day when you are drinking?"). A description of individuals with missing and inconsistent data appears in a later section.

The final sample size for the baseline time point was 310 individuals. This dataset was used for description of the baseline sample (Specific Aim #1), for regression analyses involving the prediction of baseline adherence (Specific Aim #2), and for internal consistency estimation and confirmatory factor analysis (Secondary Aim #2). This sample was also used for path analysis (Secondary Aim #1), however, six univariate outliers were removed.

The sample for repeated measures analysis (Specific Aim #3) was reduced to 287 due to the additional extraction of individuals with missing (n=3) or inconsistent (n=30) AUDIT-C data at Time 2. The sample for examining the test-retest reliability of the AUDIT-C (Secondary Aim #2) was reduced (n=88) due to the exclusive use of control subjects with complete AUDIT-C data at baseline and Time 2 data. Discussion of the impact of reduced sample sizes and generalizability of the findings follows in later sections.

3.4 VARIABLES AND MEASURES

The variables and measures for the secondary data analysis are limited to those used in the PS. ART adherence was measured with electronic event monitoring (EEM). Sociodemographic data were extracted from a comprehensive standard instrument developed by the Center for Research in Chronic Disorders at the researcher's home institution. Disease profile parameters (CD4 count, detectable/undetectable HIV RNA) and ART regimen characteristics were obtained from the PS-designed Medical Record Review. The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) was used to categorize alcohol use. All AUDIT-C data was extracted from the first three questions of the full 10-item Alcohol Use Disorders Identification Test (AUDIT) used by the PS to assess alcohol use. Drug use was assessed through drug-related questions to the AUDIT by the PS, specifically regarding the use (yes/no) and frequency of use (# days per week) of tobacco and various illicit substances: cocaine/crack, heroin, opioids, marijuana, stimulants, inhalants, and other "club drugs."

Self-efficacy was measured with the HIV Self-Efficacy Scale (SES). Depressive symptoms were assessed with the Beck Depression Inventory II (BDI-II). Social support was evaluated using the total score from the Interpersonal Support Evaluation List (ISEL), and personality characteristics were measured with each of the five scales comprising the NEO Five-Factor Inventory (NEO-FFI). A description of each variable and its respective instrument follows; please contact the PS principal investigator, Dr. Judith Erlen, for specific information about the measures.

3.4.1 Primary outcome variable

The primary outcome variable of interest was adherence. Adherence is the degree to which a patient follows or conforms to the prescribed therapeutic regimen (Sackett & Haynes, 1976); in this case, medication adherence focused on an antiretroviral (ART) regimen. Specifically, five types of medication adherence served as the primary set of ART adherence variables: dose adherence, day adherence, days under-dosing, days over-dosing, and days with null dosing. These variations on adherence were added in order to capture phenomena such as weekend "drug holidays," and over-administration of medications, especially as toxicity issues may be particularly salient for individuals with impaired hepatic function due to alcohol use and/or hepatitis B/C co-infection. Table 1 describes the five adherence variables and their mode of calculation in the PS.

In each case, adherence was treated as a continuous variable and was measured by EEM (MEMS 6 TrackCap, AARDEX, Ltd.) for the randomly selected "monitored drug." EEM uses a special medication container cap which electronically records and stores each time the cap on the

medication bottle is opened. Data from the "chip" inside the cap is downloaded to a computer program for analysis by the researcher. In the PS, raw data from the EEM caps were downloaded, visually reviewed, and arranged for analysis by the PS staff. Pocket dosing data from participants' medication diaries were inserted, where applicable. The PS statistician then created and applied analytic algorithms for the specific types/categories of adherence, and performed adherence analysis.

Table 1: ***Definition and calculation of adherence variables-A***

Adherence variable	Definition	Calculation
Dose adherence	% of medication administrations	Doses taken/doses prescribed
Day adherence	% of days with correct # of pills taken	Days correct/total number of days prescribed
Days under-dosing	% of days with less than prescribed number of administrations taken	Days taking less than prescribed/total number of days prescribed
Days over-dosing	% of days with more than prescribed number of administrations taken	Days taking more than prescribed/total number of days prescribed
Days with null dosing	% of days with no medication administrations at all	Days taking no doses during a 24 hour period/total number of days prescribed

3.4.2 Primary independent variable

3.4.2.1 Alcohol screening status

The primary independent variable, *alcohol screening status*, had two separate dimensions based on participant responses to the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) (Bush, et al., 1998). The first dimension of alcohol screening status involved categorization as AUDIT-C positive or AUDIT-C negative for *at-risk drinking*. This classification is consistent with the NIAAA approach used in alcohol screening algorithms for clinicians, where individuals are considered "at-risk drinkers" if they have a positive alcohol screen on a self-report tool such as the AUDIT or AUDIT-C, or if they endorsed having one or more heavy drinking days ($\geq$5 drinks/day for men, $\geq$4 drinks/day for women) (NIAAA, 2005, p. 5). It is important to recognize that this categorization of *at-risk drinking* includes individuals with alcohol abuse/dependence disorders as well as individuals with hazardous drinking patterns.

In the current study, determination of AUDIT-C positive/negative status was based on total AUDIT-C score. Men with total AUDIT-C scores $\geq$4, and women with total scores $\geq$3 were classified as "AUDIT-C positive" and those with scores below the threshold were considered "AUDIT-C negative" (Bradley et al., 2003; Bradley et al., 2007; Reinert & Allen, 2007).

The second dimension of alcohol screening status, AUDIT-3 positive versus AUDIT-3 negative for at-risk drinking, captured "binge" drinking. Participants were classified as AUDIT-3 positive or negative based on their individual scores for this item, which ranged from 0 to 4. Participants with AUDIT-3 scores of zero (i.e., the "never" response) were categorized "AUDIT-3 negative," while participants with AUDIT-3 scores from 1 (less than monthly) to 4 (daily or almost daily) were considered "AUDIT-3 positive" (Bradley et al., 2007; Gordon, et al., 2001).

3.4.2.2 The Alcohol Use Disorders Identification Test--Consumption (AUDIT-C)

The AUDIT-C is an abbreviated version of the Alcohol Use Disorders Identification Test (AUDIT), the instrument used by the PS to assess alcohol use. Initially developed by the World Health Organization as a screening tool for the detection of "hazardous and harmful drinking patterns" in primary care patients, the full AUDIT assesses the conceptual domains of alcohol consumption (3 questions), alcohol dependence (3 questions), and alcohol-related consequences or problems (4 questions) over the past year (Babor, et al., 2001). The AUDIT-C consists of the first three, consumption-related items from the full 10-item AUDIT, and assess frequency of drinking, number of drinks per drinking occasion, and frequency of binge drinking ($\geq$6 drinks/occasion) over the past year. Based on 5 Likert-style response alternatives, a range of 0-4 points is possible for each item; total scores are calculated by summing the three items and thus range from 0-12.

Sensitivity and specificity ranges for the AUDIT-C depend on the diagnostic standard (alcohol abuse, alcohol dependence, hazardous drinking, at-risk drinking) and cut point used ($\geq$3, $\geq$4, $\geq$5), however, for the detection of hazardous drinking and active alcohol abuse/dependence, the sensitivity and specificity of the AUDIT-C parallels or exceeds that of comparable instruments used in clinical and research settings (e.g., standard quantity/frequency questions, CAGE, full AUDIT) (Bush, et al., 1998; Bradley et al., 2003; Bradley et al., 2007; Gordon, et al., 2001; Frank, et al., 2008). For any alcohol use disorder or risk drinking, at a cut point of $\geq$4, sensitivities generally range from 0.76-0.99, and specificities from 0.65-0.98. A cut point of $\geq$5 provides somewhat decreased sensitivity (range= 0.63-0.91), with slightly increased specificity (range = 0.83-0.98) (Reinert & Allen, 2007). Based on numerous sensitivity and specificity analyses, AUDIT-C cut-off scores of 3 for women and 4 for men have been recommended for

the detection of alcohol misuse (Bradley et al., 2003; Bradley et al., 2007; Reinert & Allen, 2007).

In the interest of clinical expediency (i.e., save time and reduce reliance on scoring schemes), the third question on the AUDIT-C which addresses episodic heavy/binge drinking ("AUDIT-3") has generated interest as a single-item alcohol screening question; it generally demonstrates slightly lower, but highly adequate sensitivities when used alone (Bradley et al., 2003; Bradley et al., 2007; Gordon, et al., 2001).

Other psychometric evaluations of the AUDIT-C are limited, and to date, none have been conducted using samples of PWHIV. In general, test-retest reliabilities of 0.98 over a 3-4 week interval, and 0.57-0.85 over a 3-month interval have been reported (Bergman & Kallman, 2002; Bradley et al, 1998). Additionally, internal consistencies (Cronbach's alphas) ranging from 0.56-0.91 have been reported (Maisto, Conigliaro, McNeil, Karemer, & Kelley, 2000; Reinert & Allen, 2007; Shields, Guttmannova, & Caruso, 2004;). In the current study, internal consistency of the AUDIT-C was excellent, with an estimate of .838 for the total sample. By subgroup, estimates were higher for females (.851) than for males (.831), and higher for whites (.851) than for nonwhites (.828).

3.4.3 Additional independent variables—confounders and covariates

3.4.3.1 Sociodemographic, disease-related, and drug use variables

Sociodemographic data were extracted from a comprehensive standard instrument developed by the Center for Research in Chronic Disorders at the researcher's home institution. Disease profile parameters (CD4 count, detectable/undetectable HIV RNA) and ART regimen characteristics

were obtained from the PS-designed Medical Record Review. The PS added drug-related questions to the AUDIT, specifically regarding the use (yes/no) and frequency of use (number of days per week) of tobacco and various illicit substances: cocaine/crack, heroin, opioids, marijuana, stimulants, inhalants, and other "club drugs." These questions were intended for descriptive purposes only and thus have not undergone psychometric evaluation; they were used descriptively in the current study in order to characterize polysubstance use in the sample.

3.4.3.2 Self-efficacy for ART adherence

Self-efficacy is defined as "beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments" (Bandura, 1997, p. 3) , i.e., antiretroviral medication adherence. The HIV Self-Efficacy Scale (SES) was used to measure self-efficacy for ART-taking at the ordinal level as an exploratory, and potentially mediating independent variable. The PS developed this 26-item tool because at the time, no comparable measure could be found related to the use of protease inhibitors. Participants are asked to rate their confidence from 1 (not at all confident) to 10 (totally confident) in their ability to take their monitored medication as prescribed during the week, at work, a party, etc., as well as some general questions regarding their perceived ability to follow the overall medication regimen. Total scores and two subscale scores (Self-efficacy Beliefs and Outcome Expectancy) can be calculated. In each case, higher scores indicate greater self-efficacy. In the current study only HIV-SES total scores were used; the internal consistency (Cronbach's alpha) for the total score was 0.947 for the total sample, at baseline (n=288).

3.4.3.3 Depressive symptoms

Depression encompasses a wide variety of symptoms such as sadness, self-dislike, indecisiveness, and concentration difficulty. The 21-item Beck Depression Inventory II (BDI-II) (Beck, Steer, & Brown, 1996) was used to assess the degree of self-reported depressive symptoms, the third exploratory independent variable. Assessing depressive symptomatology over the previous 2 weeks, the BDI-II yields ordinal level data where each item is scored from 0-3, with higher scores indicating greater depressive symptoms. While total score cut-points are properly set based on the characteristics of the sample, the general guidelines are total scores of 0-13 minimal depression; 14-19 mild depression; 20-28 moderate depression, and 29-63 severe depression. While the latest version of the BDI-II was developed to correspond with the Diagnostic and Statistical Manual of Mental Disorders—4th Edition, this tool is not meant to formally diagnose depression, but to indicate the presence and severity of depressive symptoms (Beck, 1996). Despite its widespread use in studies of PWHIV (Barroso & Sandelowski, 2001), psychometric evaluations of the BDI-II have primarily been conducted in samples of psychiatric outpatients and college students, the two populations on which the BDI-II was normed (Brantley, Dutton, & Wood, 2004). In the current study, the internal consistency (Cronbach's alpha) of the BDI-II was 0.940 for the total sample at baseline (n=299).

3.4.3.4 Social support

Social support is the perception of resources provided by others, and as an exploratory independent variable, was measured with the 40-item Interpersonal Support Evaluation List (ISEL) (Cohen, 1985). The ISEL contains four subscales which assess different dimensions of perceived social support: *Appraisal* (perceptions of having another for emotional support and to

discuss problems with); *Belonging* (the perception of having others to do things with); *Self-esteem* (the perception of having a positive evaluation when comparing one's self to others); and *Tangible* (the perception of available material aid) (Cohen, 1985). This instrument yields ordinal-level data on a 4-point Likert scale ranging from "definitely false" to "definitely true." Total and subscale scores can be calculated, with higher scores indicating greater perceived social support. While previous studies of PWHIV have used the ISEL (Catz, et al., 1999; Holmes, Bilker, Chapman, & Gross, 2007; Rogers, Hansen, Levy, Tate, & Sikkema, 2005; Weaver et al., 2005), limited psychometric data are available on its use in populations of HIV-infected persons. Cronbach's alphas for the total scale have been reported from .74 to .94 (Bastardo & Kimberlin, 2000; Rogers et al., 2005; Sikkema et al., 2000), and one medication adherence study reported a Cronbach's alpha of .82 for the Tangible subscale (Weaver et al., 2005). Internal consistency (Cronbach's alpha) for the ISEL total score and subscales scores in the current study were as follows: ISEL total score, .950 (n=294); Tangible, .877 (n=304); Self-esteem, .798 (n=300); Belonging, .865 (n=302); Appraisal, .884 (n = 307).

3.4.3.5 Personality factors

Personality consists of emotional, interpersonal, experiential, attitudinal, and motivational styles which affect mind, behavior, and action. As an exploratory independent variable, personality factors were dimensionalized and measured using the five domains of the NEO Five-Factor Inventory (NEO-FFI) (Costa & McCrae, 1992). The NEO-FFI consists of five 12-item scales addressing the domains of *Neuroticism* (negative affect, self-reproach); *Extroversion* (positive affect, sociability, activity); *Openness* (aesthetic interests, intellectual interests, unconventionality); *Agreeableness* (non-antagonistic orientation, prosocial orientation), and

Conscientiousness (orderliness, goal-striving, dependability). Higher scores indicate a greater degree of the corresponding characteristic (Costa & McCrae, 1992). Psychometric evaluations of the NEO-FFI using samples of PWHIV have not been previously reported, though the NEO-FFI and its longer, parent instrument, the NEO Personality Inventory-Revised (NEO-PI) have been recently used in studies of HIV-positive individuals (Ironson, O'Cleirigh, Weiss, Schneiderman, & Costs, 2008; Johnson & Neilands, 2007; O'Cleirigh, Ironson, Weiss, & Costs, 2007). In the current study, internal consistency estimates (Cronbach's alpha) for the NEO-FFI scales at baseline were as follows: Neuroticism, 0.853 (n=307); Extroversion, 0.796 (n=304); Openness, 0.629 (n=303); Agreeableness, 0.656 (n=306); Conscientiousness, 0.849 (n=305).

3.5 PROCEDURES

3.5.1 Human Subjects Protections

The SDA involved the study of existing data which were de-identified by the PS data manager according to guidelines established by the Complete Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study thus met criteria for Exemption-4 status under Health and Human Services regulations in 45 CFR 46.101(b)(4), and was granted exempt approval by the University of Pittsburgh Institutional Review Board (IRB) (Appendix C). The PS was previously approved by the University of Pittsburgh IRB and other site boards. All PS participants provided written informed consent.

3.5.2 Data preparation

The PS collected data longitudinally at five time points, however, only baseline and Time 2 (post-intervention—3 months) data were used for the SDA. All PS data were collected from 2003-2008, and were coded and processed using Teleform Designer^{TM}, a Windows-based software for automated data entry/verification which can be used to input scannable, precoded forms, and to verify the incoming data against investigator-set parameters. This process reduces the likelihood of data entry errors and ensures data quality. Data sets by measure were de-identified and extracted from the PS master database/server and merged into a common file for analysis by the PS data manager using SPSS, version 15.0 (SPSS Inc., 1989-2004).

3.5.3 Data screening

All screening and analytic procedures were also conducted in SPSS by the principal investigator. Missing data analysis, outlier examination, and checking of statistical assumptions were performed prior to analysis.

Univariate and multivariate outlier analyses were performed by group, i.e., AUDIT-C positive/negative and AUDIT-3 positive/negative status, and by variable for the extent of their impact. In order to reduce the influence of extreme univariate outliers, the highest three scores for dose adherence (scores >155% where mean=79%) were score altered, as were the three lowest scores the HIV Self-efficacy Scale total score (scores below 55, where mean=216) (Tabachnick & Fidell, 2001). The inherent statistical assumptions for each analytic strategy (i.e., the normality, linearity, homoscedasticity, and independence of residuals; and absence of

multicollinearity/singularity) were assessed using univariate descriptive statistics and visual plots (e.g., histograms, partial plots). Due to the violation in the assumption of normality, in all analyses by AUDIT-C and AUDIT-3 status, reflected square root transformations were applied to the dose and day adherence variables, and a regular square root transformation was applied to days under-dosing. Additionally, the days over-dosing adherence variable could not be suitably transformed, and was dichotomized as adherent/nonadherent using a 1-day cut point (i.e., over-dosing 1 or more days during the 14 day assessment period was considered nonadherent; this is equivalent to a score of 7.14% on the continuous EEM measure of adherence).

Missing data analysis was conducted to determine the frequency and patterns of any missing values. As the number of cases with missing data for each of the psychosocial and sociodemographic variables was small (i.e,, 3-6), only complete cases were used. The situation was more complex with respect to the primary outcome variable (adherence) and the primary independent variables (AUDIT-C and AUDIT-3 status. As the implications of these issues vary by analysis, a brief summary is provided here, with more detailed analysis and discussion appearing in later sections where the impact is most significant.

Individuals with missing AUDIT data at baseline were omitted from the analysis because they could not be categorized for the main independent variables. Similar issues related to *inconsistent* AUDIT data were described earlier; in some respects, this data could also be considered missing because these individuals were omitted from the sample. More detailed evaluation of the inconsistent AUDIT data appears in section 5.3.3.2. AUDIT and/or adherence data were also missing at Time 2, primarily affecting analyses like AUDIT-C test-retest reliability in Secondary Aim #2 and Specific Aim #3 which tested the effect of the PS adherence interventions. More detailed evaluation of these problems thus appears in section 6.1.2.

3.6 STATISTICAL ANALYSIS

3.6.1 Primary Aim #1

Descriptive statistics (i.e., measures of central tendency and variability for continuous variables; frequency distributions for categorical variables; parametric and nonparametric correlations) were used to characterize the sample. These measures ensured the appropriate selection of statistical analysis procedures, allowed for characterization of the sample in terms of sociodemographic, substance use, psychosocial, and disease/regimen factors; and allowed for the examination of bivariate relationships between these variables. Bivariate analyses were performed to identify possible confounders and covariates of the relationship between alcohol screening status and each type of adherence. Given the non-normal distribution of the majority of variables, Mann Whitney U tests were used to assess the degree of association between continuous variables and each of the two sets of alcohol screening statuses. Chi square tests of independence, the Fisher exact test, and the Spearman rank correlation coefficient were used for categorical variables. An alpha level of .05 was used for all tests. Additionally, internal consistency was estimated for the AUDIT-C, HIV-SES, BDI-II, NEO-FFI, and ISEL, particularly given the limited data on the use of several of these multi-item self-report tools in samples of PWHIV.

3.6.2 Primary Aim #2

A series of sequential multiple linear regression analyses were performed in order to determine if AUDIT-C positive status and AUDIT-3 positive status improved the prediction of each ART adherence pattern after controlling for various sociodemographic, drug use, and psychosocial variables. Regression analyses were conducted only for adherence variables demonstrating significant or trend results in initial Mann Whitney U testing; no further analysis of days with null dosing was performed as it was highly insignificant (this finding was not unexpected given that days with null dosing is subsumed under the larger category of days under-dosing). Separate regression analyses were performed by group (AUDIT-C positive/negative, AUDIT-3 positive/negative) for each of the four remaining adherence variables, first, controlling for confounding variables, then, controlling for confounding variables and covariates.

For model entry, potential sociodemographic, drug use, and psychosocial confounding variables were required to demonstrate a significant or trend ($\leq$.10) relationship in bivariate analysis with both AUDIT-C status and the given type of adherence, or with both AUDIT-3 status and the given type of adherence. The following variables entered one or both sets of original regression models as potential *confounders*: CD4 count; crack use yes/no, marijuana use yes/no; Agreeableness score (NEO-FFI), conscientiousness score (NEO-FFI), and HIV Self-Efficacy Scale total score. Significant confounding variables were then entered as a single block into a backward regression model [p-IN (.05) p-OUT (.10)]; confounding variables significant at this step were then retained as the first block, with AUDIT-C status entered as the second block.

A similar, but separate set of analyses then allowed both potential confounders and covariates to enter the models. For model entry, variables were considered potential *covariates*

if, in bivariate analysis, they demonstrated a significant or trend (<.10) relationship with the adherence outcome variable of interest only. In addition to the aforementioned potentially confounding variables, the following variables entered one or both of the initial regression models as potential covariates: age, race (white/nonwhite), HIV viral load detectable/undetectable, CD4 count, and health insurance status (insured/uninsured). All confounder and confounder-covariate models were estimated hierarchically using adjusted R-squared and parameter estimates with confidence intervals, and model assessment strategies included residual, outlier, and influential case analysis.

3.6.3 Primary Aim #3

Repeated measures analysis (e.g. covariance pattern models using linear mixed modeling methods) was used in order to determine if alcohol screening status impacts the effect of the adherence interventions on dose adherence over time, i.e., baseline to 12 weeks follow-up. Alcohol screening status was represented in the same manner described for Primary Aim #1, however, to assess possible moderation by AUDIT-C screening status on the relationship between the intervention and dose adherence, an interaction term between group and AUDIT-C screening status (AUDIT-C positive/negative) was included in the repeated measures model, with AUDIT-C negative status serving as the reference group. Main effects (treatment group, time, AUDIT-C status), 2-way interactions (treatment group X time, treatment group X AUDIT-C status, AUDIT-C status X time), and the possible 3-way interaction (treatment group X time X AUDIT-C status) were estimated in the model. Again, models were estimated hierarchically and subsequent model assessment strategies included residual, outlier, and influential case analyses.

Models were re-run with different nested covariance structures (compound symmetry, AR1, Toeplitz, and unstructured) and compared using Akaike's Information Criterion (AIC), where the lowest AIC indicated the best fit. An alpha level of .05 was used for all tests.

3.6.4 Secondary Aim #1

Path analysis was used to identify the role of ART adherence self-efficacy as a potential mediator of the relationship between baseline dose adherence and depressive symptoms, social support, and conscientiousness, while considering alcohol screening status as a potential *moderator* of any mediational relationship(s). Exploring mediation (i.e., the "how" and "why" of the relationship between variables) is most appropriate when the case can be made for relatively strong relationships between the predictors and the criterion variable (Baron, 1986); as previously indicated, depressive symptoms, social support, and to a lesser extent, personality characteristics, have demonstrated relationships to health regimen adherence. To test mediation in this study, models considering both the direct (unmediated) effect of each of the predictors on adherence, as well as their indirect effects through self-efficacy were fitted. In order to assess possible moderation by alcohol screening status (AUDIT-C positive/negative) on any mediational relationships, interaction terms between AUDIT-C status and depressive symptoms, social support, and conscientiousness were generated for inclusion in the final mediational models.

Baron and Kenny's (1986) three criteria for mediation served as the standard to be met, i.e., 1) variations in levels of depressive symptoms, social support, and conscientiousness will significantly account for variations in self-efficacy, 2) variations in self-efficacy will

significantly account for variations in dose adherence, and 3) when these paths are controlled, any previously significant relationship between depressive symptoms, social support, conscientiousness, and dose adherence will diminish in magnitude, ideally becoming insignificant, where approaching zero provides stronger evidence for principal mediation by self-efficacy. As recommended by several authors (Kenny, 2008; MacKinnon, 2002; Preacher & Hayes, 2004; Sobel, 1990) the Sobel test was also performed in order to confirm the statistical significance of any mediational effects evidenced by these criteria. The SPSS macro for the Sobel test (with bootstrapping) developed by Preacher and Hayes (2004) was used. Due to violations in the assumption of normality, reflected square root transformations were satisfactorily applied to dose adherence and self-efficacy.

As the sample size of individuals screening AUDIT-C positive was relatively modest, the aim was considered exploratory, and only path analysis models were considered where individual measured variables were used. Verification of the assumptions of interval-level data, one-way casual flow in the model, multivariate normality, absence of outliers, linearity, the absence of multicollinearity/singularity, and residuals small and centered around zero (Tabachnik & Fidell, 2001) were nonetheless evaluated.

3.6.5 Secondary Aim #2

Internal consistency of the AUDIT-C was estimated using Cronbach's alpha. Due to non-normal distribution of AUDIT-C total scores at the baseline and 12 week (3 month) time points, the test-retest reliability of the AUDIT-C was determined using the Wilcoxon signed-rank test. Because alcohol use could have feasibly been impacted by the adherence interventions (particularly the

individualized intervention), only participants from the control group with complete AUDIT-C data at both time points were used in the test-retest estimation for the AUDIT-C (n=88).

Multi-sample confirmatory factor analysis (CFA) (Byrne, 1989; Joreskog, 1979) was used to examine the hypothesized single factor structure of the AUDIT-C, first using the entire sample of PWHIV, then using cross-validation samples based on gender (male/female) and race/ethnicity (white/nonwhite). Specifically, a single, invariant factor pattern and invariant factor loadings were hypothesized across males and females and across whites and nonwhites. Baseline models were estimated for each group, followed by a series of confirmatory factor analyses which used means and variance adjusted weighted least squares (WLSMV) estimation. (This approach is most appropriate for small sample sizes and for categorical data.) Models for each group were tested hierarchically; factor structures and factor loadings were then constrained to be equal (invariant) across gender and racial groups and these more restrictive models were compared to the baseline model(s). Model evaluation and goodness of fit were assessed with multiple criteria, e.g., chi square statistic, Root Mean Square Error of Approximation (RMSEA), and Weighted Least Square Mean Residual (WRMR). Goodness-of-fit was indicated by a nonsignificant chi square statistic, RMSEA values < .05 - .08, and WRMR values < .90 (Loehlin, 2004; Muthen & Muthen, 2007).

4.0 MANUSCRIPT #1—THE PREDICTION OF HIV ANTIRETROVIRAL MEDICATION ADHERENCE BY POSITIVE SCREENS ON THE ALCOHOL USE DISORDERS IDENTIFICATION TEST—CONSUMPTION (AUDIT-C)

NOTE: This is a pre-publication version of this manuscript; please contact the primary author prior to citation.

4.1 ABSTRACT

Background: Alcohol use appears to negatively impact antiretroviral (ART) adherence, though conclusions about its effects are inconsistent, and the mechanisms of these effects are unclear. Accurate, efficient assessment of alcohol risk behavior is thus an important issue, particularly for adherence counseling in HIV/AIDS. The primary aim of this study was to determine if positive screening results on the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) and its single binge-related question (AUDIT-3) predicted ART adherence. Methods: A secondary data analysis was conducted using data from a randomized controlled trial which tested the efficacy of two cognitive-behavioral ART adherence interventions over time and tracked medication adherence with electronic event monitoring. A series of sequential multiple linear regression analyses were performed to determine if positive alcohol screening results

added to adherence prediction after controlling for various biopsychosocial factors. Results: In models controlling for confounding variables, a positive AUDIT-C screen significantly added to the prediction of dose adherence (p=.013) and days under-dosing (p=.023). A positive screen on the AUDIT-3 did not predict any type of adherence. When potential covariates also entered the models, prediction of dose adherence, day adherence, and days under-dosing by AUDIT-C status and AUDIT-3 status improved. AUDIT-C status again significantly predicted dose adherence (p=.005) and days under-dosing (p=.021), with a trend towards prediction of days over-dosing (p=.089). AUDIT-3 status demonstrated trend significance for predicting dose adherence (p=.086). Conclusions: The AUDIT-C shows potential as a screening tool for the identification of at-risk drinking and, indirectly, for ART nonadherence. Additional study is needed on the interrelationships between alcohol, adherence, personality and self-efficacy.

4.2 INTRODUCTION

Because of its direct relationship to successful viral suppression, antiretroviral (ART) medication adherence is a critical component of self-management in HIV/AIDS, and adherence is associated with multiple interwoven patient-, medication-, disease-, environment-, and system-related factors (2008 NIH guidelines). While substance use is among these predictors and correlates of ART adherence, until recently, researchers exploring the effects of substance use on ART adherence have focused on the impact of illicit drug use (Chander, Himmelhoch et al., 2006). Subsequently, there is an incomplete and inconsistent understanding of the overall impact of alcohol on adherence. Full understanding of the interplay between alcohol use,

sociodemographic, clinical, and other adherence-related psychosocial factors such as drug use, depression, social support, self-efficacy, and personality is also limited. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has identified alcohol use as a probable "key determinant" in ART adherence, and has called for research efforts to 1) focus on a greater "understanding of the multidimensionality of the relationship between alcohol use and abuse and adherence," and 2) to focus on improving medication adherence among PWHIV who use and abuse alcohol (Bryant, 2006, pp. 1492-1493).

This call for additional research is warranted for several reasons. Alcohol use is common among persons with HIV/AIDS (PWHIV); 40-55% of PWHIV acknowledge some degree of alcohol use (Chander, Lau et al., 2006; Galvan et al., 2002; Lucas et al., 2002; Tucker et al., 2003), and 10-20% of these individuals consume alcohol at hazardous or harmful levels (Arnsten et al., 2002; Braithwaite et al., 2005; Chander, Lau et al., 2006; Conigliaro et al., 2006; Cook et al., 2001; Galvan et al., 2002; Halkitis et al., 2003; Lucas et al., 2002; Samet, Horton, et al., 2004; Tucker et al., 2003; Waldrop-Valverde et al., 2006). Considerable but inconclusive evidence exists regarding alcohol's deleterious effects on viral replication, immune suppression, central nervous system impairment, progression of comorbid illnesses, the effectiveness and toxicity of ART, and ART adherence (Bryant, 2006).

While numerous investigators have found that alcohol consumption at all levels appears to negatively impact adherence (Braithwaite et al., 2005; Chander, Lau et al., 2006; Cook et al., 2001; Halkitis et al., 2003; Parsons, Golub, et al., 2007; Samet, Horton, et al., 2004; Tucker et al., 2003), other researchers report conflicting or mixed findings (Arnsten 2002, Berg 2004, Halkitis 2005, Waldrop-Valverde, 2006, Hinkin, 2004, Paterson, 2000). Significant methodological differences across studies, i.e., differences in the definition and assessment of

alcohol use and adherence (Chander, 2006), leave unanswered questions about the extent to which alcohol predicts adherence over and above the impact of sociodemographic, psychosocial, and illicit drug use factors. Resolving these gaps and incongruities is important given that alcohol is clearly a significant risk behavior in the overlapping clinical realms of HIV/AIDS treatment and progression.

Accurate, efficient assessment of alcohol risk behavior is thus an important issue for HIV/AIDS care providers, particularly with respect to individualized ART adherence counseling (Cook, 2001; Conigliaro et al., 2003; Petry 1999; Samet, Phillips, et al., 2004). One alcohol screening instrument with the advantages of brevity and sensitivity is the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) (Bush et al., 1998). The AUDIT-C is an alcohol screening tool based on the first three (consumption-related) items from the full 10-item Alcohol Use Disorders Identification Test (AUDIT), a screening questionnaire developed by the World Health Organization and validated internationally for the detection of "hazardous and harmful drinking patterns" (Babor et al., 2001). The sensitivity and specificity of the AUDIT-C for the detection of hazardous drinking and active alcohol abuse/dependence parallels or exceed that of comparable instruments used in clinical and research settings (e.g., standard quantity/frequency questions, CAGE, full AUDIT) (Bradley et al., 2003; Bradley et al., 2007; Bush et al., 1998; Frank et al., 2008; Gordon et al., 2001). Additionally, the third question on the AUDIT-C which addresses episodic heavy/binge drinking (AUDIT-3) generally demonstrates slightly lower, but highly adequate sensitivities when used alone as a single alcohol screening question (Bradley et al., 2003; Bradley et al., 2007; Gordon et al., 2001). Because of its psychometric properties and the ease of its administration and scoring, the AUDIT-C is one of the alcohol screening tools

recommended by the NIAAA; a single screening question similar to the AUDIT-3 is also recommended (NIAAA, 2005).

Interestingly, scores on the AUDIT-C and the AUDIT-3 have also been directly associated with the incidence of other health-related outcomes such as risk of hospitalizations for gastrointestinal conditions such as liver disease, upper GI bleeds, and pancreatitis (Au et al., 2007) and general 5-year mortality rates (Bradley, et al., 2001). Given these findings, a reasonable question is whether the AUDIT-C and AUDIT-3 might also help predict health behaviors such as ART adherence. While various versions of the AUDIT have been used by adherence researchers for assessing alcohol use, no published study has heretofore considered the potential for this type of dual purpose. If positive screens on the AUDIT-C are predictive of ART adherence, the detection of both risk behaviors could potentially be improved in the context of a regular alcohol screening program. In particular, increased attention to the intersection of alcohol use and chronic medical illness would remind clinicians to be alert to the greater risk of suboptimal adherence in those who screen positive for at-risk drinking.

The overall purpose of this study was to determine if alcohol use predicts specific patterns of ART adherence behavior. The primary aim was to determine if positive screening results on the AUDIT-C and/or AUDIT-3 provide additional prediction of ART dose adherence based on electronic event monitoring (EEM), including day adherence, days under-dosing, days over-dosing, and days with null dosing after controlling for various sociodemographic, substance use, and psychosocial variables.

4.3 MATERIALS AND METHODS

4.3.1 Parent Study Overview

This study is an analysis of existing data from the randomized controlled trial entitled "Improving Adherence to Antiretroviral Therapy" (R01-NR04749), National Institute of Nursing Research, Principal Investigator, Dr. Judith Erlen. The "parent study" (PS) tested the efficacy of two cognitive-behavioral ART adherence interventions over time and examined the impact of adherence on clinical outcomes and quality of life. Parent study data were collected in two phases from 1998-2002 (Phase I) and from 2003-2008 (Phase II). This study uses baseline data from Phase II.

Parent study participants were randomized to a structured adherence intervention condition, individualized adherence intervention condition, or usual care, and were provided with an electronic event monitor (EEM) and a medication bottle. For a one month induction period, PS participants used the EEM and medication bottle for a randomly selected ART medication in their regimens (i.e., the monitored drug). Participants also maintained medication diaries, recording time of medication removal, time of medication ingestion, and any instances of pocket dosing. Data from the last 2 weeks of this induction period were considered the baseline adherence assessment and were used to determine PS participants' general medication adherence status. Individuals with perfect adherence at baseline (i.e., "100% adherers") were extracted for separate analysis by the PS and were not randomized to the aforementioned treatment conditions.

4.3.2 Participants/setting

Parent study participants were required to be ≥ 18 years old, on combination HIV therapy, administering their own medications, English-speaking, free from significant cognitive impairment, and community-dwelling with telephone access. Participants were recruited from multiple sites (a university-based clinic, community hospitals, and comprehensive care centers) in western Pennsylvania and eastern Ohio. Individuals were excluded from participation if they were living with another individual already enrolled in the study, had upper extremity or visual impairments which precluded self-administration of medication, or had hearing difficulties without adaptive telephone equipment for possible delivery of the telephone intervention.

The PS was approved by the University of Pittsburgh Institutional Review Board (IRB), and other site boards; all PS participants provided written informed consent. The current study was granted exempt approval by the University of Pittsburgh IRB because it involved the study of existing data de-identified according to guidelines established by the Complete Health Insurance Portability and Accountability Act (HIPAA) of 1996.

4.3.3 Measures

4.3.3.1 Primary outcome variable

The primary outcome variable of interest was ART adherence. More specifically, five types of medication adherence served as the primary set of ART adherence variables: dose adherence, day adherence, days under-dosing, days over-dosing, and days with null dosing. Table 2 describes the five adherence variables and their mode of calculation in the PS. In each case,

Table 2: ***Definition and calculation of adherence variables-B***

Adherence variable	Definition	Calculation
Dose adherence	% of medication administrations	(Number of doses taken/number of doses prescribed) * 100
Day adherence	% of days with correct # of pills taken	(Number of days with the correct number of doses/total number of days prescribed) * 100
Days under-dosing	% of days with less than prescribed number of administrations taken	(Number of days taking less than prescribed/total number of days prescribed) * 100
Days over-dosing	% of days with more than prescribed number of administrations taken	(Number of days taking more than prescribed/total number of days prescribed) * 100
Days with null dosing	% of days with no medication administrations at all	Days taking no doses during a 24 hour period/total number of days prescribed

adherence was treated as a continuous variable and was measured by EEM (MEMS 6 TrackCap, AARDEX, Ltd.) for the monitored drug. EEM uses a special medication container cap which electronically records and stores each time the cap on the medication bottle is opened. Data from the "chip" inside the cap is downloaded to a computer program for analysis by the researcher. In the PS, raw data from the EEM caps were downloaded, visually reviewed, and arranged for analysis by the PS staff. Pocket dosing data from participants' medication diaries were inserted,

as necessary, and when possible. The PS statistician then applied programmed analytic algorithms for the specific types/categories of adherence to yield the adherence summary indices for analysis.

4.3.3.2 Independent variable—Alcohol screening status

The primary independent variable, *alcohol screening status*, had two separate dimensions based on participant responses to the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) (Bush, 1998). The first dimension of alcohol screening status involved categorization as AUDIT-C positive or AUDIT-C negative for *at-risk drinking*. This classification is consistent with the NIAAA approach used in alcohol screening algorithms for clinicians, where individuals are considered "at-risk drinkers" if they have a positive alcohol screen on a self-report tool such as the AUDIT or AUDIT-C, or if they endorsed having one or more heavy drinking days ($\geq$5 drinks/day for men, $\geq$4 drinks/day for women) (NIAAA, 2005, p. 5). It is important to recognize that this categorization of *at-risk drinking* includes individuals with alcohol abuse/dependence disorders as well as individuals with hazardous drinking patterns.

In the current study, determination of AUDIT-C positive/negative status was based on total AUDIT-C score. Men with total AUDIT-C scores $\geq$4, and women with total scores $\geq$3 were classified as "AUDIT-C positive" and those with scores below the threshold were considered "AUDIT-C negative" (Bradley et al., 2003; Bradley et al., 2007; Reinert & Allen, 2007).

The second dimension of alcohol screening status, AUDIT-3 positive versus AUDIT-3 negative for at-risk drinking, captured "binge" drinking. Participants were classified as AUDIT-3 positive or negative based on their individual scores for this item, which ranged from 0 to 4. Participants with AUDIT-3 scores of zero (i.e., the "never" response) were categorized "AUDIT-

3 negative," while participants with AUDIT-3 scores from 1 (less than monthly) to 4 (daily or almost daily) were considered "AUDIT-3 positive" (Bradley et al., 2007; Gordon, 2001).

4.3.3.3 The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C)

The AUDIT-C is an abbreviated version of the Alcohol Use Disorders Identification Test (AUDIT), the instrument used by the PS to assess alcohol use. Initially developed by the World Health Organization as a screening tool for the detection of "hazardous and harmful drinking patterns" in primary care patients, the full AUDIT assesses the conceptual domains of alcohol consumption (3 questions), alcohol dependence (3 questions), and alcohol-related consequences or problems (4 questions) over the past year (Babor, 2001). The AUDIT-C consists of the first three, consumption-related items from the full 10-item AUDIT, and assess frequency of drinking, number of drinks per drinking occasion, and frequency of binge drinking ($\geq$6 drinks/occasion) over the past year. Based on 5 Likert-style response alternatives, a range of 0-4 points is possible for each item; total scores are calculated by summing the three items and thus range from 0-12.

Sensitivity and specificity ranges for the AUDIT-C depend on the diagnostic standard (alcohol abuse, alcohol dependence, hazardous drinking, at-risk drinking) and cut point used ($\geq$3, $\geq$4, $\geq$5); however, for the detection of hazardous drinking and active alcohol abuse/dependence, the sensitivity and specificity of the AUDIT-C parallels or exceeds that of comparable instruments used in clinical and research settings (e.g., standard quantity/frequency questions, CAGE, full AUDIT) (Bush, 1998; Bradley et al., 2003, 2007; Gordon, 2001; Frank, 2008). Based on numerous sensitivity and specificity analyses, AUDIT-C cut-off scores of 3 for women and 4 for men have been recommended for the detection of alcohol misuse (Bradley et al., 2003;

Bradley et al., 2007; Reinert & Allen, 2007). In the current study, internal consistency of the AUDIT-C was excellent, with an estimate of .838 for the total sample. By subgroup, estimates were slightly higher for females (.851) than for males (.831), and slightly higher for whites (.851) than for nonwhites (.828).

In the interest of clinical expediency (i.e., save time and reduce reliance on scoring schemes), the third question on the AUDIT-C which addresses episodic heavy/binge drinking ("AUDIT-3") has generated interest as a single-item alcohol screening question; it generally demonstrates slightly lower, but highly adequate sensitivities when used alone (Bradley et al., 2003; Bradley et al., 2007; Gordon, 2001).

4.3.3.4 Additional independent variables

Sociodemographic data were extracted from a comprehensive standard instrument developed by the Center for Research in Chronic Disorders at the University of Pittsburgh School of Nursing. *Disease profile parameters* (CD4 count, detectable/undetectable HIV RNA) and *ART regimen characteristics* were obtained from the PS-designed medical record review.

Drug use was assessed through questions related to the frequency of use for tobacco and various illicit substances (marijuana/hashish, cocaine, crack, heroin, "ecstasy," "poppers," stimulants, opioids, hallucinogens, inhalants) which were added to the full AUDIT by the PS. For the current analysis, responses to the drug use items were dichotomized as "use" / "no use" for each drug. Additionally, a composite drug use score was created by summing the number of "use" responses (excluding tobacco) for each participant, reflecting the total number of illicit substances used.

Several psychosocial variables previously demonstrated to be related to adherence were also assessed. *Self-efficacy*, "beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments" (Bandura, 1997, p. 3), was assessed using the 26-item HIV Self-Efficacy Scale (SES) developed by the PS to measure self-efficacy for ART medication-taking. At PS inception, no comparable measure could be found related to assessing self-efficacy for taking protease inhibitors. Participants were asked to rate their confidence from 1 (not at all confident) to 10 (totally confident) in their ability to take their monitored medication as prescribed during the week, at work, a party, etc., as well as some general questions regarding their perceived ability to follow the overall medication regimen. An overall total score and two subscale scores (Self-efficacy Beliefs and Outcome Expectancy) can be calculated. In each case, higher scores indicate greater self-efficacy. In the current study only total HIV-SES scores were used; the internal consistency (Cronbach's alpha) for the total score was .947 for the sample, at baseline (n=288). For males, Cronbach's alpha for the total score was .951 (n = 198) and was slightly lower for females (.938, n = 90). Across race, Cronbach's alpha for the total score for whites was .951 (n = 118), and was slightly lower for nonwhites at .944 (n = 170).

Depressive symptoms were measured with the Beck Depression Inventory II (BDI-II), a 21-item tool which assesses depressive symptomatology over the previous 2 weeks, and which was developed to correspond with the Diagnostic and Statistical Manual of Mental Disorders—4th Edition (Beck, 1996). While total score cut-points are properly set based on the characteristics of the sample, total scores of 0-13 suggest minimal depression; 14-19 mild depression; 20-28 moderate depression, and 29-63, severe depression. The internal consistency of the BDI-II, based on Cronbach's alpha, was .940 for the total sample at baseline (n=299). For males, Cronbach's alpha for the total score was .941 (n = 205) and was slightly lower for females

(.939, n = 94). Across race, Cronbach's alpha for the total score for whites was .951 (n = 118), and was slightly lower for nonwhites at .944 (n = 170).

Personality characteristics were measured using the 5 domains of the NEO Five-Factor Inventory (NEO-FFI) (Costa & McCrae, 1992). The NEO-FFI consists of five 12-item scales addressing the domains of *Neuroticism* (anxiety, hostility, depression, impulsiveness); *Extroversion* (positive affect, assertiveness, activity, gregariousness); *Openness* (aesthetic interests; receptivity to feelings, new experiences, ideas, actions, and values); *Agreeableness* (trust, altruism, straightforwardness, modesty), and *conscientiousness* (competence, order, self-discipline, achievement striving) (Costa & McCrae, 1992). Higher scores indicate a greater degree of the corresponding characteristic; scale scores are not summed to produce a total score.

In the current study, internal consistency estimates (Cronbach's alpha) for the NEO-FFI scales at Baseline were as follows: Neuroticism, .853 (n = 307); Extroversion, .796 (n = 304); Openness, .629 (n = 303); Agreeableness, .656 (n = 306); Conscientiousness, .849 (n = 305). By gender, internal consistency estimates (Cronbach's alpha) for the NEO-FFI scales at Baseline were as follows for males: Neuroticism, .855 (n = 211); Extroversion, .791 (n = 210); Openness, .665 (n = 207); Agreeableness, .670 (n = 210); Conscientiousness, .851 (n = 210). For females, internal consistency estimates (Cronbach's alpha) for the NEO-FFI scales at Baseline were as follows: Neuroticism, .852 (n = 96); Extroversion, .806 (n = 94); Openness, .536 (n = 96); Agreeableness, .637 (n = 96); Conscientiousness, .846 (n = 95). By race, internal consistency estimates (Cronbach's alpha) for the NEO-FFI scales at Baseline were as follows for whites: Neuroticism, .900 (n = 127); Extroversion, .836 (n = 127); Openness, .721 (n = 126); Agreeableness, .708 (n = 126); Conscientiousness, .841 (n = 127). For nonwhites, internal consistency estimates (Cronbach's alpha) for the NEO-FFI scales at Baseline were as follows:

Neuroticism, .802 (n = 180); Extroversion, .762 (n = 177); Openness, .512 (n = 177); Agreeableness, .608 (n = 180); Conscientiousness, .857 (n = 178).

Social support was measured with the Interpersonal Support Evaluation List (ISEL) (Cohen, 1985). The ISEL contains 40 Likert-style items which assess different dimensions of perceived social support: *Appraisal* (perceptions of having another for emotional support and to discuss problems with); *Tangible* (the perception of available material aid); *Self-esteem* (the perception of having a positive evaluation when comparing one's self to others); and *Belonging* (the perception of having others to do things with) (Cohen, 1985). Total and subscale scores can be calculated, with higher scores indicating greater perceived social support. Only total ISEL scores were used in the current study.

Internal consistency (Cronbach's alpha) for the ISEL total score and subscales scores in the current study at baseline were as follows: ISEL total score, .950 (n = 294); Tangible, .877 (n = 304); Self-esteem, .798 (n = 300); Belonging, .865 (n = 302); Appraisal, .884 (n = 307). By gender, internal consistency estimates for males were as follows at baseline: ISEL total score, .948 (n = 205); Tangible, .872 (n = 210); Self-esteem, .792 (n = 209); Belonging, .864 (n = 209), Appraisal, .878 (n = 211). For females, internal consistency estimates were as follows at baseline: ISEL total score, .955 (n = 89); Tangible, .888 (n = 94); Self-esteem, .809 (n = 91); Belonging, .867 (n = 93); Appraisal, .894 (n = 96). By race, internal consistency estimates for whites were as follows at baseline: ISEL total score, .961 (n = 120); Tangible, .911 (n = 127); Self-esteem, .834 (n = 123); Belonging, .895 (n = 209); Appraisal, .918 (n = 128). Internal consistency estimates for nonwhites were as follows at baseline: ISEL total score, .940 (n = 174); Tangible, .843 (n = 177); Self-esteem, .768 (n = 177); Belonging, .839 (n = 179); Appraisal, .940 (n= 174).

4.3.4 Procedures

4.3.4.1 Data preparation and screening

Datasets by measure were de-identified and extracted from the PS master database and merged into a common file for analysis by the PS data manager using SPSS, version 15.0 (SPSS Inc., 1989-2004). All data screening and analytic procedures were also conducted in SPSS by the principal investigator. Missing data analysis, outlier examination, and checking of statistical assumptions were performed prior to analysis.

For the current study, no sampling exclusions were made based on race, gender, ethnicity, or sexual orientation; however, only randomized participants from the PS were included, i.e., individuals deemed "100% adherers" were omitted from the current analysis (n=8), as were individuals who were removed from medications by their physicians during the induction phase (n=2) and individuals who did not return the EEM cap at the end of the induction phase (n=2).

Because missing or inconsistent responses on AUDIT items 1-3 would impede categorization of individuals as AUDIT-C positive/negative and/or AUDIT-3 positive/negative, PS participants with missing (n=6) or inconsistent (n=18) AUDIT data on these items at baseline were removed from the sample prior to analysis. Inconsistent responses included, for example, a response of "never" to AUDIT question 1 ("How often do you have a drink containing alcohol?") and the selection of a quantity greater than zero in response to AUDIT question 2 ("How many drinks containing alcohol do you have on a typical day when you are drinking?"). Four individuals were removed for missing or incomplete adherence data at baseline. The final sample size was comprised of 310 individuals.

4.3.4.2 Univariate and bivariate analyses

Descriptive statistics (i.e., measures of central tendency and variability for continuous variables, frequency distributions for categorical variables) were used to characterize the sample. In order to reduce the influence of extreme univariate outliers, the highest three scores for dose adherence (scores >155%) and the three lowest scores for the HIV Self-efficacy Scale total score (31, 44, and 54) were score adjusted (Tabachnick & Fidell, 2001). The three dose adherence scores were decreased to 129%, just slightly higher than the next-highest score of 128.57. The three Self-efficacy Scale total scores were increased to 90, 91, and 92, respectively, just slightly higher than the next-lowest score of 93.

Bivariate analyses were performed to identify possible confounders and covariates. Given the non-normal distribution of the majority of variables, Mann Whitney U tests were used to assess the degree of association between continuous variables and each of the two alcohol screening status measures. Chi square tests of independence, Fisher's exact test, and Spearman's rank-order correlation coefficient were used for categorical variables with each of the two alcohol screening variables. Across analyses, p-values <.05 were considered statistically significant.

4.3.4.3 Main analyses

A series of sequential multiple linear regression analyses were then performed in order to determine if AUDIT-C positive status and AUDIT-3 positive status improved the prediction of each ART adherence pattern after controlling for various sociodemographic, drug use, and psychosocial variables. Regression analyses were conducted only for adherence variables demonstrating significant or trend results in initial Mann Whitney U testing; no further analysis

of days with null dosing was performed as it was highly insignificant (this finding was not unexpected given that days with null dosing is subsumed under the larger category of days under-dosing, and given that this variable had extremely limited variability). Separate regression analyses were performed by group (AUDIT-C positive/negative, AUDIT-3 positive/negative) for each of the four remaining adherence variables, first, controlling for confounding variables, then, controlling for confounding variables and covariates. Due to violation in the assumption of normality of the residuals, in all analyses by AUDIT-C and AUDIT-3 status, reflected square root transformations were applied to the dose and day adherence variables, and a square root transformation was applied to days under-dosing.

For model entry, potential sociodemographic, drug use, and psychosocial confounding variables were required to demonstrate a significant or trend ($p \leq .10$) relationship in bivariate analysis with both AUDIT-C status and the given type of adherence, or with both AUDIT-3 status and the given type of adherence. The following variables entered one or both sets of original regression models as potential *confounders*: health insurance status (insured/uninsured); CD4 count; crack use yes/no; marijuana use yes/no; Agreeableness score (NEO-FFI); conscientiousness score (NEO-FFI); and HIV Self-Efficacy Scale total score. Significant confounding variables were then entered as a single block into a backward regression model using a p-value of .10 for excusion; confounding variables that were significant at this step were then retained as the first block, with AUDIT-C or AUDIT-3 status entered as the second block.

A similar, but separate set of analyses then allowed both potential confounders and covariates to enter the models. For model entry, variables were considered potential *covariates* if, in bivariate analysis, they demonstrated a significant or trend (<.10) relationship with the adherence outcome variable of interest only. The following variables entered one or both of the

initial regression models as potential covariates in a single block which included any significant confounding variables from the previous analyses: age, race (white= 0, nonwhite = 1), HIV viral load (undetectable = 0, detectable = 1), and CD4 count, and health insurance status (uninsured = 0, insured =1). All confounder and confounder-covariate models were estimated hierarchically yielding adjusted R-squared values and parameter estimates with 95% confidence intervals. Model assessment strategies included residual, outlier, and influential case and sensitivity analyses. For all analyses, p-values <.05 were considered statistically significant.

Additionally, the days over-dosing adherence variable was substantially negatively skewed and could not be suitably transformed. It was dichotomized as adherent/nonadherent using a 1-day cut point (i.e., over-dosing 1 or more days during the 14 day assessment period was considered nonadherent; this is equivalent to a score of 7.14% on the continuous EEM measure of adherence).

4.4 RESULTS

4.4.1 Univariate and bivariate analysis

A series of tables present characteristics of the total sample, and by AUDIT-C status. Table 3 presents sociodemographic and clinical characteristics. Table 4 presents a profile of alcohol and drug use. Adherence and psychosocial characteristics are presented in Table 5. The total sample was approximately two-thirds male, over half self-identified as Non-white ethnicity, and the median age was 44 years old. Mean AUDIT-C score was 2.16 (*SD*= 2.59); 27.1% and 34.2% of

the total sample were classified as AUDIT-C positive and AUDIT-3 positive, respectively. Compared to AUDIT-C negative participants, AUDIT-C positive individuals had significantly fewer years of formal education; were significantly more likely to have health insurance; significantly more likely to use drugs overall and to use marijuana, crack, cocaine, "poppers," hallucinogens, and tobacco; had significantly more depressive symptoms; had significantly higher neuroticism scores, lower agreeableness and conscientiousness scores; had significantly less social support; and had significantly lower dose adherence, days under-dosing, and days over-dosing. Additionally, AUDIT-C positive individuals were slightly less likely to use stimulants, use opioids, and have lower day adherence ($.05 < p < .10$) compared to AUDIT-C negative participants.

By AUDIT-3 status, groups were significantly different in essentially parallel fashion (data not shown), with additional differences noted for sex, and a trend difference noted for English as primary language ($.05 < p < .10$). AUDIT-3 positive individuals were significantly more likely to be men and slightly more likely to be insured. Significant differences in dose adherence and day adherence were detected by AUDIT-3 positive versus negative status, with a trend relationship for days under-dosing noted. Additionally, in contrast to AUDIT-C status, only trend differences ($p<.10$) emerged for stimulant use and depressive symptoms ($.10 < p > .05$), while differences in opioid use were nonsignificant.

Individuals with inconsistent AUDIT-C data at either time point (n = 48) were significantly less likely to have health insurance, χ^2 (1, N = 344) = 7.313, p = .013; significantly more likely to use opioids, χ^2 (1, N = 339) = 5.777, p = .037; and had significantly higher conscientiousness scores (p = .026) compared to individuals with consistent AUDIT-C data.

Additionally, those with inconsistent AUDIT-C data were slightly more likely to use hallucinogens, χ^2 (1, N = 339) = 3.672, p = .089.

Table 3: ***Sociodemographic and clinical characteristics of the sample***

		Total sample (n=310)	AUDIT-C positive (n=84)	AUDIT-C negative (n=226)	p†
Sex	Male	68.4%	73.8%	66.4%	.211
	Female	31.6%	26.2%	33.6%	
Race	White	41.3%	40.5%	41.6%	.859
	Nonwhite	58.7%	59.5%	58.4%	
	More than one race	2.6%	3.6%	2.2%	
Age	Mean	43.51	42.54	43.89	.127
	SD	7.78 44.00	7.68	7.81	
	Median		43.00	44.00	
Years formal education (n = 309)	Mean	13.01	12.46	13.22	.001
	SD	2.90	3.09	2.80	
	Median	12.00	12.00	13.00	
Primary language	English	98.1%	100%	97.3%	.195
	Other	1.9%		2.7%	
Marital status	Currently married/partnered	20.6%	17.9%	21.7%	.460

Table 3 (continued)

Employment	Currently employed	18.1%	15.5%	19.0%	.470
	Not currently employed	81.9%	84.5%	81.0%	
Number of adults in household (n = 308)	Mean	1.67	1.51	1.73	.130
	SD	1.90	.908	2.16	
	Median	1.00	1.00	1.00	
Number of children in household (n = 307)	Mean	0.33	0.36	0.27	.356
	SD	0.80	0.83	0.72	
	Median	0.00	0.00	0.00	
Health insurance	Yes	93.2%	98.8%	91.2%	.020
	No	6.8%	1.2%	8.9%	
HIV Exposure category‡	MSM	50.4%	44.7%	52.4%	.418
	Heterosexual contact	31.2%	26.3%	33.0%	.447
	IVDU	13.5%	18.4%	11.7%	.296
	IVDU + MSM	2.1%	5.3%	1.0%	.117
	Other/Unknown	2.8%	5.2%	2.0%	.292
Viral load undetectable? (n = 294)	Yes	58.8%	61.3%	57.9%	.608
	No	41.2%	38.8%	42.1%	
CD4 count (n = 285)	Mean	458	423	472	.351
	SD	324	294	397	
	Median	389	355	334	

Table 3 (continued)

ART medication ("monitored drug")	Combivir	8.4%			
	Norvir	8.1%			
	Truvada™	7.4%			
	Reyataz™	7.1%			
Frequency of dosing for "monitored drug"	Once daily	51.0%	50.0%	51.3%	.968
	Twice daily	46.5%	47.6%	46.0%	
	Three times daily	2.5%	2.4%	2.7%	

Note. † Significance testing for differences between AUDIT-C positive /negative groups, assessed with Mann-Whitney U tests for continuous variables and chi-square tests or Fisher exact test, where appropriate.
SD= standard deviation; MSM = men who have sex with men; IVDU = intravenous drug use.
‡Results presented for individuals reporting only one exposure category, i.e., 89.2% of total sample, 90.4% of AUDIT-C positive individuals, and 86.4% of AUDIT-C negative individuals

Table 4: ***Alcohol and drug use in the sample***

		Total sample (n=310)	AUDIT-C positive (n=84)	AUDIT-C negative (n=226)	p†
Drinking status	Nondrinkers	37.7%	0%	51.8%	.000
	Drinkers	62.1%	100%	48.2%	
AUDIT-C total	Mean	2.11	5.71	.84	.000
	SD	2.59	2.13	1.02	
	Median	1.00	5.00	0.00	
AUDIT-C status	Positive	27.1%	--	--	
	Negative	72.1%	--	--	
AUDIT-3 status	Positive	34.2%	95.2%	88.5%	.000
	Negative	65.8%	4.8%	11.5%	

Table 4 (continued)

		Total sample (n=310)	AUDIT-C positive (n=84)	AUDIT-C negative (n=226)	p†
AUDIT-C Question 1					
	Never	37.7%	0.0%	51.8%	
	Monthly or less	28.4%	13.1%	34.1%	
	2-4 x/month	20.6%	40.5%	13.3%	
	2-3 x/week	7.7%	26.2%	0.9%	
	≥4x/week	5.5%	20.2%	0.0%	
AUDIT-C Question 2					
	0 drinks	37.7%	0.0%	0.0%	
	1 or 2 drinks	32.9%	16.7%	38.9%	
	3 or 4 drinks	18.4%	42.9%	9.3%	
	5 or 6 drinks	7.4%	27.4%	48.2%	
	7-9 drinks	2.3%	8.3%	0.0%	
	10 or more drinks	1.3%	4.8%	0.0%	
AUDIT-C Question 3	Never	65.8%	4.8%	88.5%	
	Less than monthly	20.3%	44.0%	11.5%	
	Monthly	8.1%	29.8%	0.0%	
	Weekly	3.5%	13.1%	0.0%	
	Daily or almost daily	2.3%	8.3%	0.0%	

Table 4 (continued)

		Total sample (n=310)	AUDIT-C positive (n=84)	AUDIT-C negative (n=226)	p†
Drug Use, Yes	Any	46.4%	69.7%	38.4%	.000
	Marijuana	34.2%	50.0%	28.3%	.000
	Crack	15.8%	29.8%	10.6%	.000
	Cocaine+	11.0%	18.1%	8.4%	.016
	Poppers	8.4%	14.3%	6.2%	.022
	Opioids	6.8%	10.7%	5.3%	.092
	Stimulants	4.2%	8.3%	2.7%	.049
	Heroin+	3.9%	2.4%	4.4%	.404
	Hallucinogens	1.6%	4.8%	0.4%	.020
	Inhalants	1.3%	1.2%	1.3%	.924
	Ecstasy	0.3%	0.0%	0.4%	.541
	Tobacco	62.6%	76.2%	42.5%	.003

Note. † Significance testing for differences between AUDIT-C positive /negative groups, assessed with Mann-Whitney U tests for continuous variables and chi-square tests or Fisher exact test, where appropriate.
+ (n = 309)

Table 5: ***Adherence and psychosocial characteristics of the sample***

		Total sample (n=310)	AUDIT-C positive (n=84)	AUDIT-C negative (n=226)	p†
% Dose adherence	Mean	79.41	70.43	82.74	.001
	SD	30.95	32.68	29.67	
	Median	92.86	82.14	92.86	
% Day adherence	Mean	59.71	52.76	62.28	.055
	SD	31.57	35.03	29.86	
	Median	71.43	50.00	71.42	
% Days null dosing	Mean	20.55	25.16	18.84	.119
	SD	26.55	30.00	25.01	
	Median	7.14	14.29	7.14	
% Days under-dosing	Mean	32.79	42.07	29.35	.008
	SD	33.16	36.65	31.17	
	Median	21.43	35.71	14.29	
% Days over-dosing	Mean	7.50	5.16	8.37	.020
	SD	10.08	5.94	11.12	
	Median	7.14	7.14	7.14	
BDI-II	Mean	16.27	18.77	15.35	.027
(Total score, n = 309)	SD	12.47	13.02	12.16	
	Median	14.00	17.00	12.00	
ISEL	Mean	75.42	70.74	77.15	.032
(Total score)	SD	23.27	22.79	23.62	
	Median	78.00	74.00	79.00	

Table 5 (continued)

		Total sample (n=310)	AUDIT-C positive (n=84)	AUDIT-C negative (n=226)	p†
Neuroticism (n = 307)	Mean	23.26	25.55	22.42	.004
	SD	8.71	8.00	8.82	
	Median	24.00	25.00	23.00	
Extroversion (n = 307)	Mean	25.74	24.90	26.05	.452
	SD	7.03	7.21	6.95	
	Median	26.00	26.00	26.00	
Openness (n = 307)	Mean	26.02	25.88	26.06	.997
	SD	5.62	5.72	5.59	
	Median	26.00	25.00	26.00	
Agreeableness (n = 307)	Mean	29.24	27.52	29.88	.001
	SD	5.49	5.23	5.46	
	Median	30.00	27.00	30.00	
Conscientiousness (n = 307)	Mean	31.36	29.99	31.88	.019
	SD	7.10	7.27	6.98	
	Median	32.00	30.00	32.50	
HIV-SES	Mean	216.16	206.02	219.91	.010
(Total score)	SD	36.66	40.00	34.70	
	Median	224.00	215.00	228.90	

Note. † Significance testing for differences between AUDIT-C positive /negative groups, assessed with Mann-Whitney U tests for continuous variables and chi-square tests or Fisher exact test, where appropriate.
SD = standard deviation

4.4.2 Multivariate analysis with confounding variables

In final regression models controlling only for potential *confounding* variables, a positive screen on the AUDIT-C predicted dose adherence and days under-dosing. Results from the final models are presented in Table 6. The overall regression equation (with confounding variables) for dose adherence was statistically significant F (3, 303) = 7.801, p = .000, and this model accounted for 7.2% of the variance in dose adherence. Both individual blocks were significant for predicting adherence. In the first block (confounding variables), crack use and conscientiousness were identified as significant predictors. As the second block, AUDIT-C status increased the model R^2 by 2%.

Similarly, the overall regression equation for days under-dosing was significant, F (2, 307) = 8.543, p = .000, and accounted for 5.3% of the variance in days under-dosing. Again, in the first block (confounding variables), self-efficacy was identified as a significant independent predictor, and as the second block, AUDIT-C status increased the model R^2 by 1.6%.

A positive screen on the AUDIT-3 did not significantly predict dose adherence, day adherence, or days under-dosing; however, a relatively similar pattern of significant independent predictors emerged by type of adherence. Results for the final models are presented in Table 7. Additionally, in logistic regression analyses, neither AUDIT-C status nor AUDIT-3 status was significantly related to the dichotomized days over-dosing variable, although a trend relationship (p = .089) was detected for AUDIT-C status (data not shown).

Table 6: ***Linear regression results for adherence predicted by AUDIT-C positive status controlling for statistically significant confounders***

			b	95% CI for b	p	R^2	$R^2\Delta$
Dose adherence[†]							
	Block 1	Crack use	.682	(.024 to 1.340)	.042		
		Conscientiousness	-.044	(-.077 to -0.11)	.010	.052	.052
	Block 2	AUDIT-C status	.685	(.148 to 1.223)	.013	.072	.020
Day adherence[†]							
	Block 1	Agreeableness	-.054	(-.109 to .002)	.059		
		Conscientiousness	-.040	(-.084 to .005)	.079		
		Self-efficacy	-.009	(-.017 to .000)	.046	.070	.070
	Block 2	AUDIT-C status	.300	(-.350 to .951)	.364	.073	.003
Days under-dosing							
	Block 1	Self-efficacy	-.015	(-.025 to -.005)	.002	.037	.037
	Block 2	AUDIT-C status	.962	(.136 to 1.788)	.023	.053	.016

Note. b = regression coefficient; CI = confidence interval; p = p-value; R^2 = correlation coefficient, squared; $R^2\Delta$ = change in R^2 with addition of AUDIT screening status in Block 2
[†]Signs of coefficients and CIs are negative due to reflected square root transformation of dose & day adherence variables. Coding of AUDIT-C status (negative = 0, positive = 1)

4.4.3 Multivariate analysis with confounding variables and covariates

When potential *covariates* were also permitted to enter the models, the ability of both AUDIT-C status and AUDIT-3 status to predict all three types of adherence was improved. Additionally, AUDIT-C status again significantly predicted dose adherence and days under-dosing, while AUDIT-3 status demonstrated trend significance for predicting dose adherence. Results from the final models are presented in Tables 8 and 9.

Table 7: ***Linear regression results for adherence predicted by AUDIT-3 positive status controlling for statistically significant confounders***

			b	95% CI for b	p	R^2	$R^2\Delta$
Dose adherence[†]							
	Block 1	CD4 count	-.001	(-.001 to .000)	.044		
		Crack use	.756	(.084 to 1.429)	.028		
		Conscientiousness	-.037	(-.071 to -.003)	.032	.069	.069
	Block 2	AUDIT-3 status	.333	(-.184 to .849)	.206	.075	.005
Day adherence[†]							
	Block 1	Agreeableness	-.054	(-.110 to .001)	.055		
		Conscientiousness	-.039	(-.084 to .005)	.080		
		Self-efficacy	-.008	(-.017 to .000)	.052	.070	.070
	Block 2	AUDIT-3 status	.283	(-.331 to .898)	.365	.073	.003
Days under-dosing							
	Block 1	Conscientiousness	-.063	(-.118 to -.008)	.026		
		Self-efficacy	-.012	(-.023 to -.001)	.032	.054	.054
	Block 2	AUDIT-3 status	.414	(-.377 to 1.204)	.304	.057	.003

Note. b = regression coefficient; CI = confidence interval; p = p-value; R^2 = correlation coefficient, squared; $R^2\Delta$ = change in R^2 with addition of AUDIT screening status in Block 2
[†]Signs of coefficients and CIs are negative due to reflected square root transformation of dose & day adherence variables. Coding of AUDIT-3 status (negative = 0, positive = 1)

In this series of regressions, the overall regression equation for dose adherence (with confounding variables and covariates) was statistically significant F (5, 286) = 8.194, p = .000, and this model accounted for 13.5% of the variance in dose adherence. Both individual blocks were significant for predicting adherence. In the first block (confounding variables plus covariates), undetectable viral load, white race, older age, and higher conscientiousness scores

remained significant independent predictors of adherence. As the second block, AUDIT-C status increased the model R^2 by 2.5%.

Similarly, the overall regression equation for days under-dosing was significant, F (4, 287) = 8.879, p = .000, and accounted for 10.9% of the variance in days under-dosing. In the first block (confounding variables + covariates), significant independent predictors of days under-dosing were detectable viral load, nonwhite race, and lower conscientiousness, and as the second block, AUDIT-C status increased the model R^2 by 1.7%.

4.5 COMMENT/CONCLUSIONS

The degree to which alcohol added to the prediction of adherence was mixed, varying by type of adherence and alcohol screening status (AUDIT-C positive/negative, AUDIT-3 positive/negative), and, according to the inclusion of confounding and covariate factors in the models. In the final models, a variety of sociodemographic, clinical, and psychosocial variables appeared as significant independent predictors of adherence.

Overall, the varied nature of these findings parallels that of existing studies on the relationship between alcohol and adherence. Other investigators who have used EEM technology have typically assessed dose adherence, and have reported significant, nonsignificant, and mixed relationships with alcohol use. Numerous EEM studies have reported alcohol consumption to be a significant independent predictor of adherence, along with factors such as race, age, and CD4 count (Golin et al., 2002; Howard et al., 2002). In another, nondrinkers over the past year had

Table 8: ***Linear regression results for adherence predicted by AUDIT-C positive status controlling for statistically significant covariates and confounders***

			b	95% CI for b	p	R^2	$R^2\Delta$
Dose adherence[†]							
	Block 1	Viral load detectable	.802	(.341 to 1.262)	.001		
		Race	.592	(.132 to 1.051)	.012		
		Age	-.030	(-.060 to -.001)	.042		
		Conscientiousness	-.048	(-.080 to -.015)	.004	.110	.110
	Block 2	AUDIT-C status	.749	(2.33 to 1.266)	.005	.135	.025
Day adherence[†]							
	Block 1	Viral load detectable	1.021	(.446 to 1.595)	.001		
		Race	.684	(.117 to 1.252)	.018		
		Agreeableness	-.051	(-.106 to .004)	.070		
		Conscientiousness	-.045	(-.089 to .000)	.048		
		Self-efficacy	-.007	(-.015 to .002)	.108	.129	.129
	Block 2	AUDIT-C status	.349	(-.302 to 1.000)	.292	.132	.003
Days under-dosing							
	Block 1	Viral load detectable	1.201	(.463 to 1.938)	.002		
		Race	1.010	(.276 to 1.743)	.007		
		Conscientiousness	-.084	(-.136 to -.032)	.002	.092	.092
	Block 2	AUDIT-C status	.978	(.151 to 1.805)	.021	.109	.017

Note. b = regression coefficient; CI = confidence interval; p = p-value; R^2 = correlation coefficient, squared; $R^2\Delta$ = change in R^2 with addition of AUDIT screening status in Block 2
[†]Signs of coefficients and CIs are negative due to reflected square root transformation of dose & day adherence variables. Coding of AUDIT-C status (negative = 0, positive = 1)

Table 9: ***Linear regression results for adherence predicted by AUDIT-3 positive status controlling for statistically significant covariates and confounders***

			b	95% CI for b	p	R^2	$R^2\Delta$
Dose adherence[†]							
	Block 1	Viral load detectable	.788	(.323 to 1.253)	.001		
		Age	-.031	(-.060 to -.001)	.041		
		Race	.595	(.132 to 1.058)	.012		
		Conscientiousness	- .050	(-.083 to -.018)	.003	.110	.110
	Block 2	AUDIT-3 status	.431	(-.061 to .922)	.086	.119	.119
Day adherence[†]							
	Block 1	Viral load detectable	1.087	(.518 to 1.657)	.000		
		Race	.677	(.108 to 1.246)	.020		
		Agreeableness	-.057	(-.112 to -.002)	.042		
		Conscientiousness	-.056	(-.098 to -.013)	.010	.119	.119
	Block 2	AUDIT-3 status	.393	(-.214 to 1.000)	.203	.124	.005
Days under-dosing							
	Block 1	Viral load detectable	1.186	(.445 to 1.928)	.002		
		Race	1.014	(.277 to 1.752)	.007		
		Conscientiousness	-.087	(-.139 to -.034)	.001	.092	.092
	Block 2	AUDIT-3 status	.622	(-.161 to 1.404)	.119	.100	.008

Note. b = regression coefficient; CI = confidence interval; p = p-value; R^2 = correlation coefficient, squared; $R^2\Delta$ = change in R^2 with addition of AUDIT screening status in Block 2
[†]Signs of coefficients and CIs are negative due to reflected square root transformation of dose & day adherence variables. Coding of AUDIT-3 status (negative = 0, positive = 1)

significantly greater odds of adherence than drinkers (Holmes, Bilker, Wang, Chapman, & Gross, 2007). However, other researchers have found no relationship between adherence and alcohol use, abuse, or dependence (Halkitis, Kutnick, & Slater, 2005; Hinkin et al., 2004; Paterson, et al., 2000). Finally, other studies with internally mixed results underscore the

presumed complexity of the alcohol-adherence relationship. For example, Arnsten and colleagues (2002) reported that alcohol use several times per week or every day was not significantly related to adherence, but significant differences in adherence did emerge between those who did/did not endorse an alcohol or drug coping style (i.e., those who endorsed using alcohol or drugs to get through problems or make themselves feel better). Berg et al. (2004) detected no significant differences in median adherence rates for those with and without problem alcohol use ($\geq$5 drinks per occasion and/or drinking several days per week or every day), however, a significant interaction emerged where women with problem alcohol use were significantly less adherent than men with problem use.

Other adherence investigators have used the AUDIT to determine study eligibility or categorize alcohol consumption patterns. Cook et al (2001) used scores of $\geq$8 on the full AUDIT to establish "hazardous drinking" patterns, and defined "binge drinking" as $\geq$6 drinks per occasion for women, and $\geq$5 drinks per occasion for women, and reported that hazardous drinking was significantly associated with self-reported taking of medications off schedule during the previous week, but not with self reports of missing a dose in the previous 24 hours. Additionally, binge drinking was not significantly associated with either taking medications off schedule or missing doses. Finally, age, race, and crack/cocaine use were also among the potential confounding variables controlled for in multivariate analyses; however, the particular variables included in each model were not specified. Parsons, Rosof, and Mustanski (2007) used a cut-off score of 8 on the full AUDIT as an inclusion criterion for their study of ART adherence among HIV+ outpatients with existing alcohol problems; however, as one of three alcohol-related factors, total AUDIT score was not significantly associated with odds of having perfect self-reported adherence over the previous 2 weeks.

While others have used alcohol screening tests, and specifically, the AUDIT, to categorize drinking patterns or generate study samples, to our knowledge, this study is the first to consider the ability of an alcohol screening test result (i.e., positive/negative) to predict medication adherence. The brevity of the AUDIT-C and the AUDIT-3 (compared to the full AUDIT and other alcohol screening instruments) make them particularly appealing for widespread use by direct care providers. The AUDIT-C and AUDIT-3 show potential as indirect screening tools for both at-risk drinking and ART nonadherence, understanding that by nature, this screening function implies the need for further, more in-depth evaluation of both behavior sets. Importantly, the AUDIT-C is a screening instrument for hazardous and harmful drinking; it is designed to be sensitive at the potential expense of specificity, and is not diagnostic for alcohol abuse or dependence. Importantly, because this study sought to examine the impact of at-risk drinking on ART adherence (a wider spectrum than simply alcohol abuse and dependence disorders), we used the lower set of gender-specific scoring thresholds for the AUDIT-C, i.e., $\geq$4 for men and $\geq$3 for women (Bradley et al; 2003; Reinert & Allen, 2007).

The lower ability of the AUDIT-3 to provide additional prediction of adherence was somewhat surprising; given its embeddedness within the AUDIT-C, greater sensitivity for predicting adherence would be expected compared to the AUDIT-C. Despite a precedent having being set for the dichotomization of the AUDIT-3 in the manner selected (i.e., essentially, binge ever/never in the past year) (Bradley, 2007; Gordon, 2001), a different cut point, e.g., "within the last 3 months" (Williams & Vinson, 2001) may have yielded greater sensitivity for the detection of an effect on adherence. Additionally, other proponents of single question alcohol screening have noted improvements in sensitivity for the detection of hazardous drinking and/or alcohol use disorders when such questions are modified to inquire about $\geq$5 drinks per occasion for men

and ≥4 drinks for women (Bradley et al., 2003; Williams & Vinson, 2001). However, as this study was an analysis of existing data, such adjustments were not feasible in the current analyses.

In the current study, the nonsignificant relationship between alcohol and some of the adherence variables is potentially attributable to differential effects of alcohol on different aspects of medication-taking; correspondingly high degrees of conscientiousness and/or self-efficacy (despite at-risk drinking patterns); or inherent constraints of the data or methods used. However, still another possible explanation involves consideration of perceptions and attitudes about alcohol use and ART. For example, one qualitative investigation of beliefs about alcohol, ART, and HIV disease progression found heavy drinkers to be significantly less likely to perceive drinking alcohol with ART as harmful, and less likely to indicate that they would skip or miss their medication if they had been drinking (Sankar et al, 2007). In turn, heavy drinkers may not be skipping or missing ART doses, and would thus, by EEM accounts, be represented as adherent.

The emergence of conscientiousness and self-efficacy as significant independent predictors of adherence deserves comment. First, low conscientiousness has previously been associated with both alcohol use (Hopwood et al., 2007; Martin & Scher, 1994; Loukas, Krull, Chassin, & Carle, 2000) and HIV disease progression. Using the NEO-FFI, O'Cleirigh, Ironson, Weiss, and Costa (2007) found conscientiousness to be significantly related to change in both CD4 count and viral load level over a one year time span, however, neither adherence nor depression significantly mediated these relationships. Using the NEO Personality Inventory—Revised (NEO-PI-R), the longer, parent instrument to the NEO-FFI, the same team also found conscientiousness to be significantly associated with slower rates of viral load increase over a longer, 4-year time span (Ironson, O'Cleirigh, Weis, Schneiderman, & Costa, 2008). These

findings, in conjunction with significant correlations between conscientiousness and missed ART doses as well as between conscientiousness and depression, social support, and cocaine/other substance, have raised the possibility that conscientiousness exerts its influence on HIV/AIDS disease progression through other meditational pathways which incorporate these variables, including alcohol use (O'Cleirigh, Ironson, Weiss, & Costa, 2007; Ironson, O'Cleirigh, Weis, Schneiderman, & Costa, 2008). Our findings further suggest the presence of interactions between conscientiousness, viral load, and alcohol use and further substantiate the need for meditational analyses to explore the specific mechanisms through which adherence, alcohol/substance use, psychosocial, and disease-related factors exert their influence on one another.

Secondly, across studies, self-efficacy consistently predicts ART adherence (Ammassari, 2002). (Catz et al., 2000; Cha et al., 2007; Halkitis et al., 2005; Johnson et al., 2006; Luszczynska et al., 2007; Simoni et al., 2006). The often concomitant appearance of self-efficacy and conscientiousness as independent predictors of adherence speaks to their partial conceptual overlap. However, the two concepts do address different dimensions of individual behavior; self-efficacy is task-specific and reflects *confidence* or *beliefs* about one's ability to perform a given behavior, while conscientiousness reflects a more global personality orientation reflecting *attributes* such as self-discipline, competence, order, and dependability. Self-efficacy may have failed to appear as an independent predictor of dose adherence due to the broad, relatively coarse calculation of this type of adherence. Another possible explanation is that the measure of self-efficacy used in this study (i.e., HIV Self-efficacy Scale total score, as opposed to the more specific self-efficacy beliefs scale of the same measure) reduced the precision with which self-efficacy could be measured.

The results of this study require consideration of several limitations. First, because of the small number of AUDIT-C positive individuals (n = 84) versus AUDIT-C negative individuals (n = 224), power was limited to detect differences in sociodemographic, psychosocial, and adherence variables by alcohol status group. In a similar vein, the effect sizes for the regression analyses with statistically significant results were small, ranging from .0102 – .0289, reflecting that alcohol screening status explained only an additional 1-3% of the variance in adherence after controlling for confounders and/or covariates. The corresponding clinical significance varies according to the medication regimen considered. For example, assuming a twice-daily one pill regimen and the two week assessment period, each pill would represent 3.57% of the dose adherence score. Detecting an effect size of .02 would thus mean that AUDIT-C status explained a difference equal to less than half of a pill. Additionally, with the exception of AUDIT-C status predicting dose adherence after controlling for confounders and covariates (the most highly significant result), most of the analyses were underpowered to detect such small changes in the amount of variance added to the prediction of adherence by AUDIT-C. For most analyses (depending on the number of predictors in the model), the detectable effect size for achieving adequate power (80%) needed to be .025.

Because substance use was not an initial primary variable of interest in the PS, the amount of variability in the sample in terms of alcohol and drug use was relatively low. Secondly, because of its purpose as a screening test, the AUDIT-C is designed to be sensitive at the expense of specificity; therefore, the number of individuals who screened positive on the AUDIT-C may have been inflated. The use of gender-specific cut-offs may also have increased the number of false-positive screens in this study. In contrast, however, the inclusion of nondrinkers in the analysis, i.e., those with total scores of zero on the AUDIT-C, may have

artificially increased specificity. Similar considerations apply to the designation of AUDIT-3 positive individuals. Issues related to over-sensitivity of the AUDIT-C are potentially less problematic in the clinical setting, where the aim might be to capture as many individuals with at-risk drinking patterns as possible for further alcohol evaluation or individualized adherence counseling. Finally, AUDIT-C and AUDIT-3 responses were extracted from responses to the full AUDIT. While other investigations have shown that in this format, the AUDIT-C does have high levels of sensitivity and specificity for at-risk drinking and alcohol use disorders (Dawson, 2005; Gordon, 2001), participant responses may have been different were these items administered independently of the remaining AUDIT items and drug-related questions.

Several characteristics of the sample underscore the extent to which these findings may be generalized; first is the relatively high mean rates of adherence at baseline (79.43 $\pm$ 31.63), though similar rates of mean dose adherence (70-80%) have been reported in other ART adherence studies which have used EEM (Hinkin, 2004; Golin, 2002; Paterson, 2000). Additionally, participants were individuals engaged in care, and highly motivated to participate in a long-term adherence trial. The general rate of alcohol consumption (63.3%) appears to be higher than rates of alcohol use among PWHIV reported previously, which range from 40-55% (Galvan, 20002; Tucker, 2003; Conigliaro, Justice, Gordon, & Bryant, 2006; Arnsten et al., 2002; Chander Lau, & Moore, 2006; Samet, Horton, Meli, Freedberg, & Palepu, 2004, Cook et al., 2001). Placing the sample's rates of AUDIT-C positive (27.1%) and AUDIT-3 positive (34.2%) individuals in the context of previous research is considerably more challenging due to wide variation in definition and determination of alcohol use patterns. Alcohol consumption may be categorized in terms of quantity/frequency ("moderate," "frequent," "heavy" drinking), risk ("at-risk/risky" drinking) or consequences ("problematic" drinking); in terms of DSM-IV

alcohol use disorders e.g., abuse/dependence), or subsumed under the broader variable of "substance abuse." Again, in extant studies, rates of hazardous use and/or binge use generally range from 10-20% (Cook et al., 2001; Chander, Lau, & Moore, 2006; Conigliaro, 2003), but have been reported as high as 30% (Berg et al., 2004). Given the AUDIT-C's identity as a screening tool, and that fact that it specifically inquires about alcohol use over the past year, the higher rates of hazardous and binge use in this sample are not surprising.

Future investigations should consider sampling strategies for improved variability in alcohol consumption patterns, the use of a modified AUDIT-3 question as described above, and the use of a non-derived format of the AUDIT-C and/or the AUDIT-3. Future studies may also be enhanced through the use of self-report adherence data in conjunction with the use of EEM technology. While EEM is often considered the "gold standard" in terms of reliable and objective adherence assessment, and is more highly correlated with viral load and CD4 count, it relies on the assumption that cap openings reflect medication ingestion, and its cost often makes its use prohibitive in research as well as clinical practice. The use of multiple assessment modalities is often recommended as the ideal approach for explaining the greatest amount of variance in adherence (Berg & Arnsten, 2006; Pearson, Simoni, Hoff, Kurth, & Martin, 2007).

A more nuanced understanding of the influence of alcohol on medication-taking, and accurate detection of problematic alcohol use and/or adherence carry additional implications for clinicians. What does improved understanding and detection mean for counseling the individual patient about both alcohol use and adherence? In one study, interviews with these patients' HIV care providers revealed that clinician rates of addressing alcohol consumption and ART varied widely as did the specific advice given (Sankar et al., 2007). Additionally, NIH guidelines for the use of antiretrovirals make limited mention of any direct impact of alcohol on ART outside of

recommendations to avoid the use of alcohol with Abacavir, and general recommendations for individuals with hepatitis B and/or hepatitis C co-infection to avoid alcohol due to increased risk of hepatoxicity (2008 NIH Use of ART guidelines--web). Collectively, these findings are not surprising given the inconclusive nature of the research on alcohol's effects on viral replication, immune suppression, cognitive function, comorbid illness, and ART effectiveness (Bryant, 2006), and underscore the need for tandem investigations on the biophysical impact of alcohol use in the context of HIV/AIDS.

5.0 MANUSCRIPT #2—AN EVALUATION OF THE PSYCHOMETRIC PROPERTIES AND FACTOR STRUCTURE OF THE AUDIT-C IN PERSONS WITH HIV/AIDS

NOTE: This is a pre-publication version of this manuscript; please contact the primary author prior to citation.

5.1 ABSTRACT

Background: The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) is widely endorsed as a brief alcohol screening instrument for primary care patients, however, examinations of its psychometric properties and factor structure have been limited, particularly across gender and racial subgroups, and in persons with HIV/AIDS (PWHIV). Methods: AUDIT-C data were extracted from a randomized controlled trial which looked at the effect of an antiretroviral medication adherence intervention over time in PWHIV. Internal consistency and 3-month test-retest reliability were estimated using Cronbach's alpha, the Spearman-Brown coefficient, and Wilcoxon rank-sum test. Indirect validity analysis of those with inconsistent AUDIT-C responses was performed with logistic regression. Multi-sample confirmatory factor analyses (CFAs) were conducted to replicate a single factor structure of the AUDIT-C and

evaluate its consistency across gender and racial (white/nonwhite) subgroups. Results: The AUDIT-C demonstrated adequate internal consistency (α = .835) and test-retest reliability (*r* = .734) in the total sample and gender and racial subgroups. Wilcoxon signed-rank tests test-retest reliability were generally nonsignficant by group, suggesting the stability of AUDIT-C scores. Whites showed borderline significance (Z = - 1.96, p = .055), suggesting a score change over time. For validity checks predicting the odds of having inconsistent AUDIT-C responses, opioid users had 3 times greater odds of having inconsistent AUDIT-C data [OR = 3.139, 95% CI (.1267 – 7.777), p =.013]. Participants with higher conscientiousness scores were also more likely to have inconsistent data [OR = 1.053, 95% CI (1.006 – 1.103), p = .027]. Multi-sample confirmatory factor analysis revealed factor invariance for sex, but the best-fitting model for race allowed partial invariance where AUDIT-C item 3 (episodic heavy drinking) was free to vary across whites/nonwhites, X^2 (3, 310) = 1.818, p = .6111. Conclusion: Generally speaking, the AUDIT-C appears to be reliable in this sample of PWHIV. Researchers who modify the AUDIT-C may risk compromising validity, particularly in samples including drug users. Further attention to the cultural equivalence of the AUDIT-C may be warranted. Findings require confirmation with larger samples having greater variability in alcohol use.

5.2 INTRODUCTION

The Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) (Bush, 1998) is a derived form of the Alcohol Use Disorders Identification Test (AUDIT) developed by the World Health Organization to screen for hazardous and harmful drinking among primary care patients

(Babor, 2001; Saunders, 1993). While the complete AUDIT instrument is intended to assess three conceptually distinct factors associated with hazardous and harmful drinking, i.e., alcohol consumption, alcohol dependence, and alcohol-related consequences, the AUDIT-C was intended to be a more efficient, but equally valid tool and is thus comprised of only the first three consumption–related items from the AUDIT. Accordingly, the AUDIT-C assesses frequency of drinking, quantity of alcohol consumed on a typical drinking day, and the frequency of drinking six or more drinks on a single occasion.

The AUDIT-C is widely recommended for alcohol screening (NIAAA, 2005), and is used by the U.S. Department of Veterans Affairs. While numerous sensitivity, specificity, and general performance analyses have been conducted on the AUDIT-C (Bradley, Bush, Epler, Dobie, Davis, Sporleder, Maynard, Burman, & Kivlahan, 2003, Bradley, DeBenedetti, Volk, Williams, Frank, & Kivlahan, 2007; Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998; Dawson, Grant, & Stinson, 2005; Frank, DeBenedetti, Volk, Williams, Kivlahan, & Bradley, 2008; Gordon, Maisto, McNeil, Kraemer, Conigliaro, Kelley, & Conigliaro, 2001), limited data exist on its psychometric properties (Bradley, McDonell, Bush, Kivlahan, Diehr, & Fihn, 1998), particularly in U.S. samples; no psychometric evaluations to date have used samples of persons with HIV/AIDS (PWHIV). Furthermore, prior studies have not attempted to replicate the presumed single consumption factor of the AUDIT-C, nor attempted to ensure the stability of such a consumption factor across gender and racial groups.

The overall purpose of this study was to evaluate the reliability and factor structure of the AUDIT-C using a sample of persons with HIV/AIDS. In particular, we sought to: 1) generate reliability estimates for the AUDIT-C with attention to differences across gender and race; 2) determine if the AUDIT-C's single factor structure is consistent across males and females, and

whites and nonwhites; and 3) determine if any of the individual items on the AUDIT-C load differently for women and/or nonwhite individuals.

5.3 MATERIALS AND METHODS

5.3.1 Parent Study Overview

This study used existing data from a randomized controlled trial entitled "Adherence to Protease Inhibitors" (R01-NR04749, National Institute of Nursing Research, Principal Investigator, Dr. Judith Erlen). The "parent study" (PS) tested the efficacy of two cognitive-behavioral ART adherence interventions over time and examined the impact of adherence on clinical outcomes and quality of life, and has been previously described in an earlier manuscript under review (Sections 4.3.1 – 4.3.3).

This study used data from the Baseline and Time 2 (12 weeks-post intervention) data collection time points, collected by the PS from 2003-2008. All data were de-identified by the PS data manager according to guidelines established by the Complete Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study thus met criteria for Exemption-4 status under Health and Human Services regulations in 45 CFR 46.101(b)(4), and was granted exempt approval by the University of Pittsburgh Institutional Review Board (IRB) (Appendix C). The PS was previously approved by the University of Pittsburgh IRB and other site boards. All PS participants provided written informed consent.

5.3.2 Measures

All AUDIT-C data was extracted from the self-report version of the full AUDIT used by the PS to assess alcohol use. Scoring of the AUDIT-C is based on 5 Likert-style response alternatives. A range of 0-4 points is possible for each item; total scores thus range from 0-12. Men with total AUDIT-C scores ≥4, and women with total scores ≥3 were classified as "AUDIT-C positive" and those with scores below the threshold were considered "AUDIT-C negative" (Bradley et al., 2003; Bradley et al., 2007; Reinert & Allen, 2007). All questionnaires were completed by PS participants in mailed packets containing all of the PS measures for that time point; participants received modest remuneration for packet completion and return.

Because the AUDIT-C is comprised of only three items, individuals with missing or inconsistent AUDIT-C data at either time point were excluded from all of the current analyses. Inconsistent responses included, for example, a response of "never" to AUDIT-C question 1 ("How often do you have a drink containing alcohol?") along with the selection of a quantity greater than zero in response to AUDIT-C question 2 ("How many drinks containing alcohol do you have on a typical day when you are drinking?"). The final sample for the current study included 310 adult outpatients with HIV/AIDS from southwestern PA and northeastern OH.

Several modifications to the data were made for different analyses within the current study. First, for the current multi-sample confirmatory factor analyses (CFAs) only, AUDIT-C responses for each item were collapsed (recoded) due to small numbers of participants in some response categories (Table 10). Secondly, for analyses by gender and race, variables were coded in the following manner. Gender was dichotomized, with males serving as the reference group. PS individuals self-identified as one or more of the following races by indicating Yes/No/Don't

Know: “White,” “Black or African American,” “American Indian,” “Alaska Native,” “Native Hawaiian or other Pacific Islander,” “Asian,” or “Other.” Race was then dichotomized by the PS as white/nonwhite, with white serving as the reference group. Individuals selecting more than one race or “Other” were considered nonwhite. Consistent with NIH categorization of race/, Hispanic/Latino descent was considered an ethnicity (National Institutes of Health, 2001). Therefore, individuals self-identifying as Hispanic/Latino selected a racial background and were represented within the race categories.

Finally, the PS investigators made two modifications to the AUDIT, from which the current study’s AUDIT-C data were derived. First, in question 1, they omitted the command to skip questions 2 and 3 if the individual responded “never” to question 1. Second, they added a “0 drinks” option to question 2, which inquires about the quantity of alcohol typically consumed. Other researchers have made the similar modifications to one or more AUDIT-C questions in order to improve item response rates and improve the clarity of the questions (Bradley et al., 2003). For example, Gordon et al. (2001) removed the skip command but then replaced it because its omission had limited the number of responses to other alcohol instruments in the study. Others have added, deleted, or modified response options in questions 1 through 3 (Bush et al., 1998; Bradley et al., 1998; Bradley et al., 2003), often based on pre-testing with participants or on initial feedback early in the study (Gordon et al., 2001; Bradley et al., 1998). For example, Bradley et al. (1998) increased the final response option on question 1 from “4 or more times a week” to “6 or more times a week,” and added a “none” option to question 2. Many of these modifications are minor, but may nonetheless create additional, unanticipated problems with the data.

Data screening procedures revealed that 14% of the sample had inconsistent responses to the AUDIT-C at one or both time points. Three patterns of inconsistent data were detected in data screening. In the first pattern (81.3%), individuals acknowledged alcohol use in question 1 (e.g., endorsed drinking "2 or 4 times a month), but then selected the "0 drinks" option in question 2 which asks about the number of drinks consumed on a typical drinking day. In the second pattern (9.3%), individuals denied alcohol use in question 1 (e.g., responded "never"), but then selected a typical quantity in question 2 and/or endorsed consuming 6 or more drinks on a single occasion in question 3. In the third pattern (9.3%), individuals denied alcohol use in question 1, but endorsed some degree of binge drinking in question 3.

Because these inconsistent responses would have impeded proper categorization of individuals as AUDIT-C positive/negative and/or AUDIT-3 positive/negative by requiring the summation of potentially invalid data in order to obtain total AUDIT-C scores, PS participants with inconsistent AUDIT data were removed from all analyses. Examination of group differences between those who had any inconsistent AUDIT-C data and those who did not provided an opportunity to address the validity of the instrument as inconsistent data appeared to be at least partially related to changes made to the AUDIT by the PS.

5.3.3 Procedures

Datasets by measure were de-identified and extracted from the PS master database/server and merged into a common file for analysis using SPSS, version 15.0 (SPSS Inc., 1989-2004). Univariate statistics, internal consistency estimates via Cronbach's alpha, and test-retest analyses

via Wilcoxon signed rank test and Spearman's r were performed using SPSS. Confirmatory factor analysis using path analysis was conducted using Mplus, version 5.1 (Muthen & Muthen, 2007). The level of significance for all significance tests was set at .05.

5.3.3.1 Reliability estimates

Internal consistency of the total AUDIT-C and its individual items was estimated for the total sample and for each gender and racial group using Cronbach's alpha and the original non-collapsed responses to the AUDIT-C. Three–month test-retest reliability was estimated using Spearman's rho and the Wilcoxon signed-rank test; nonparametric tests were required due to violations in the assumptions of normality in AUDIT-C total score at both time points. Because alcohol use over time could have potentially been influenced by the PS adherence interventions (particularly the individualized intervention), only participants from the PS's usual care condition (n=88) were included in test-retest reliability analysis of the AUDIT-C.

5.3.3.2 Inconsistent AUDIT-C data analysis

A series of bivariate logistic regression models were performed in order to develop a model for the prediction of having inconsistent AUDIT-C data. In data screening, an ordinal-level code was created where individuals were classified as having consistent data (0), inconsistent AUDIT-C data at baseline (1), inconsistent data at Time 2 (2), or inconsistent data at both (3). This code was then dichotomized as Inconsistent Yes/No, where those with consistent AUDIT-C data were coded 0 and individuals with inconsistent data at any or both time points were coded 1.

Baseline sociodemographic and other variables potentially associated with lack of question comprehension were then entered into simple logistic regression models for the

prediction of having inconsistent AUDIT-C data. Univariate logistic regression analysis was performed using the following variables: gender; age; race (white/nonwhite); years of formal education; total score on the Beck Depression Inventory II (BDI-II) (Beck, 1996); the five subscale scores from the NEO-FFI Five Factor Personality Inventory (Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness) (Costa & McCrae, 1992); total score on the PS-developed HIV Self-efficacy Scale (HIV-SES); and dichotomized drug use scores (yes/no) for marijuana, cocaine, crack, heroin, opioids, ecstasy, "poppers," stimulants, hallucinogens, and inhalants. A full description of these measures is also included in the aforementioned manuscript currently under review (Sections 4.3.1 – 4.3.3). Variables reaching significance or near significance in these analyses ($p < .10$) were then simultaneously entered into a multivariate model for the derivation of odds ratios. Model fit was evaluated with the Hosmer-Lemeshow test where a good model is reflected by a nonsignificant (>.05) chi square statistic (Tabachnik & Fidell, 2001). Nagelkerke's R^2 statistic provided an estimate of the proportion of variance in having inconsistent AUDIT-C data explained by the final model. Comparison of classification tables served as an indicator of the accuracy of group membership prediction.

5.3.3.3 Confirmatory factor analysis

Only baseline AUDIT-C data were used for confirmatory factor analysis (CFA). Two separate sets of multi-sample CFAs were conducted (Byrne, 1989; Joreskog, 1969); one by gender group (male/female), one by racial group (white/nonwhite). Variance adjusted weighted least squares (WLSMV) estimation was used as the AUDIT-C is based on ordinal-level data and because the sample size was small. Baseline models using the collapsed AUDIT-C items were created for the total sample, males, females, whites, and nonwhites in order to specify the model to be

confirmed across subgroups. Factor structures and factor loadings were then constrained to be equal (invariant) across gender and racial groups and these more restrictive models were compared to the baseline model(s). Chi-square tests, Root Mean Square Error of Approximation (RMSEA), and Weighted Root Mean Square Residual (WRMR) served as goodness-of-fit indices for how well the proposed models corresponded to the data. Acceptable fit between the proposed model and the data are reflected by a nonsignificant chi-square statistic, by RMSEA values < .05 - .08, and by WRMR values < .90 (Loehlin, 2004; Muthen & Muthen, 2007).

5.4 RESULTS

In this sample of PWHIV, 68.4% of the participants were male, 31.6% were female, 41.3% were white, and 58.7% were nonwhite. Mean and median AUDIT-C scores at the two time points were identical for the total sample; *M*, 2.15 (*SD*=2.57-2.60), *Mdn*, 1.00 (Table 10). Overall, scores were significantly lower for females than for males (Mann-Whitney U = 4953.5, p = .036). Scores were also lower for nonwhites compared to whites, however, this difference was not statistically significant (Mann-Whitney U = 6069.0, p = .366). Mean AUDIT-C scores were also similar across gender and racial groups over time; however, scores demonstrated an upward trend for males and nonwhites, and a downward trend for females and whites. Response distributions for individual collapsed AUDIT-C items by racial and gender groups are shown in Table 11.

Table 10: ***Descriptive statistics for AUDIT-C scores over time by gender and racial groups (n = 233)***

	Baseline AUDIT-C total scores				Time 2 AUDIT-C total scores (3 months)			
	M	*SD*	*Mdn*	Range	*M*	*SD*	*Mdn*	Range
Total sample (n = 233)	2.15	2.60	1.00	12	2.15	2.57	1.00	12
Males (n = 158)	2.38	2.17	2.00	12	2.44	2.64	2.00	12
Females (n = 75)	1.67	2.30	1.00	12	1.55	2.33	1.00	12
Whites (n= 93)	2.34	2.77	2.00	12	2.17	2.56	1.00	12
Nonwhites (n = 140)	2.02	2.49	1.00	12	2.14	2.59	1.00	12

Note. Data presented are based on the 233 individuals with complete AUDIT-C data at both time points

Table 11: ***Response distributions of collapsed AUDIT-C responses by gender and racial groups***

AUDIT-C item†	Collapsed response options	Total n = 310	Males n=212	Females n=98	p‡	Whites n=128	Nonwhites n=182	p+
Item 1—Frequency of drinking								
	Never	37.7%	32.6 %	49.0 %	.024	34.4 %	40.1 %	.337
	Monthly	28.4%	36.3 %	25.5 %		33.6 %	32.4 %	
	2-4 x/month	20.6%	17.9 %	19.4 %		18.8 %	18.1 %	
	≥2x/week	13.2%	13.2 %	6.1 %		13.3 %	9.3 %	
Item 2—Quantity consumed on typical drinking day								
	0 drinks	37.7%	32.5 %	49.0 %	.016	34.4 %	40.1 %	.622
	1-2 drinks	32.9%	28.8 %	27.6 %		32.0 %	25.8 %	
	3-4 drinks	18.4%	23.6 %	14.3 %		18.0 %	22.5 %	
	5 or more drinks	11.0%	15.1 %	9.2 %		15.6 %	11.5 %	
Item 3—Frequency of 6 or more drinks on single occasion								
	Never	65.8%	61.8 %	74.5 %	.081	67.2 %	64.8 %	.433
	Less than monthly	20.3%	22.2 %	16.3 %		21.9 %	19.2 %	
	Monthly or more	13.9%	16.0 %	9.2%		10.9 %	15.9 %	

Note. † (Bush et al., 1998).

‡ p-values represent significance level of chi square statistic for differences by gender for each item on the AUDIT-C.
+ p-values represent significance level of chi square statistic for differences by race for each item on the AUDIT-C.

5.4.1 Reliability estimates

5.4.1.1 Internal consistency

Overall, internal consistency of the AUDIT-C was high, with an estimate of .838 for the total sample. By subgroup, estimates were slightly higher for females (.851) than for males (.831), and slightly higher for whites (.851) than for nonwhites (.828) (Table 12 and Table 13, respectively).

Table 12: ***Internal consistency, inter-item correlations, and item-total correlations for the AUDIT-C by gender group***

Males α = .831			
AUDIT-C Items	(1)	(2)	(3)
(1)	1.000		
(2)	.829	1.000	
(3)	.877	.782	1.000
Item-Total Correlation	.639	.689	.790
Females α = .851			
AUDIT-C Items	(1)	(2)	(3)
(1)	1.000		
(2)	.931	1.000	
(3)	.916	.857	1.000
Item-Total Correlation	.727	.722	.776

Note. α = Cronbach's alpha

Table 13: ***Internal consistency, inter-item correlations, and item-total correlations for the AUDIT-C by racial group***

Whites α = .851			
AUDIT-C Items	(1)	(2)	(3)
(1)	1.000		
(2)	.869	1.000	
(3)	.894	.812	1.000
Item-Total Correlation	.669	.735	.809
Nonwhites α = .828			
AUDIT-C Items	(1)	(2)	(3)
(1)	1.000		
(2)	.854	1.000	
(3)	.901	.814	1.000
Item-Total Correlation	.664	.669	.778

Note. α = Cronbach's alpha

5.4.1.2 Test-retest reliability

Baseline and Time 2 AUDIT-C total scores were significantly correlated at the .01 level (2-tailed) for the total sample (r_s = .734), males (r_s = .785), females (r_s = .620), whites (r_s = .897), and nonwhites (r_s = .649). Notably, correlations between scores at the two time points were lower for females than for males and for nonwhites versus whites.

Wilcoxon signed-rank tests for total AUDIT-C scores from baseline and Time 2 were nonsignficant for the total sample (Z = - .643, p = .524), males (Z = - .009, p = .996), females (Z = - .947, p = .350), and nonwhites (Z = - .368, p = .721), suggesting the stability of AUDIT-C

scores over time in these groups. Results for whites, however, showed borderline significance (Z = - 1.96, p = .055), suggesting that the two sets of scores in this group increased over time.

5.4.2 Inconsistent AUDIT-C data analysis

Data screening procedures revealed that 14% of the sample had inconsistent responses to the AUDIT-C at one or both time points. In the simple logistic regression models, only three variables were associated with having inconsistent AUDIT-C data. Participants who used opioids (morphine, methadone, codeine, oxycodone) had almost 3 times greater odds of having inconsistent AUDIT data [OR = 2.863, 95% CI (1.175 – 6.974), p =.021] compared to non-users, while participants with higher conscientiousness scores had slightly lower odds [OR = 1.048, 95% CI (1.002-1.096), p = .041] of having inconsistent AUDIT-C data. A trend was also detected where hallucinogen users had greater odds of having inconsistent data [OR = 3.813, 95% CI (.881-16.510), p = .073].

Opioid use, hallucinogen use, and conscientiousness score were then entered into a multiple logistic regression model for the prediction of having inconsistent AUDIT-C data. Hallucinogen use no longer demonstrated a trend toward greater odds of having inconsistent AUDIT-C data and was dropped from the model. In the final model, non-use of opioids and higher conscientiousness were again significant predictors of having inconsistent data; opioid users had over 3 times greater odds of having inconsistent AUDIT-C data [OR = 3.139, 95% CI (.1267 – 7.777), p =.013], while those with higher conscientiousness scores also had greater odds of having inconsistent data compared to those with lower conscientiousness scores [OR = 1.053, 95% CI (1.006 – 1.103), p = .027]. The Hosmer-Lemeshow test indicated that the model was

nonsignificant, indicating a good fit between the model and the data, X^2 (7, n = 336) = 2.961, p = .889. While the model correctly predicted 85.4% of the cases having inconsistent AUDIT-C data, blindly estimating the percentage of cases would yield an even higher percentage (85.7%).

5.4.3 Confirmatory factor analysis

Because of the small number of items on the AUDIT-C (3), CFA baseline models for all four groups were "just identified," reflecting minimally sufficient data to conduct the analyses because the number of data points and the number of parameters (i.e., covariances and correlations) were the same as the number of items. The result of being "just identified" is a trivially perfect fit to the data, as indicated by the chi square tests of model fit that are equal to 0.000, with zero degrees of freedom, p-values of 0.000, as occurred with these data in each of the four models. Additionally, RMSEA and WRMR values were also all 0.000.

Across baseline models however, the collapsed AUDIT-C items were moderately well correlated (r = .782 - .931) and consistently loaded heavily onto a single factor, with factor loadings ranging from .878 - .998 (Table 14). All factor loadings were above .70 and were considered significant.

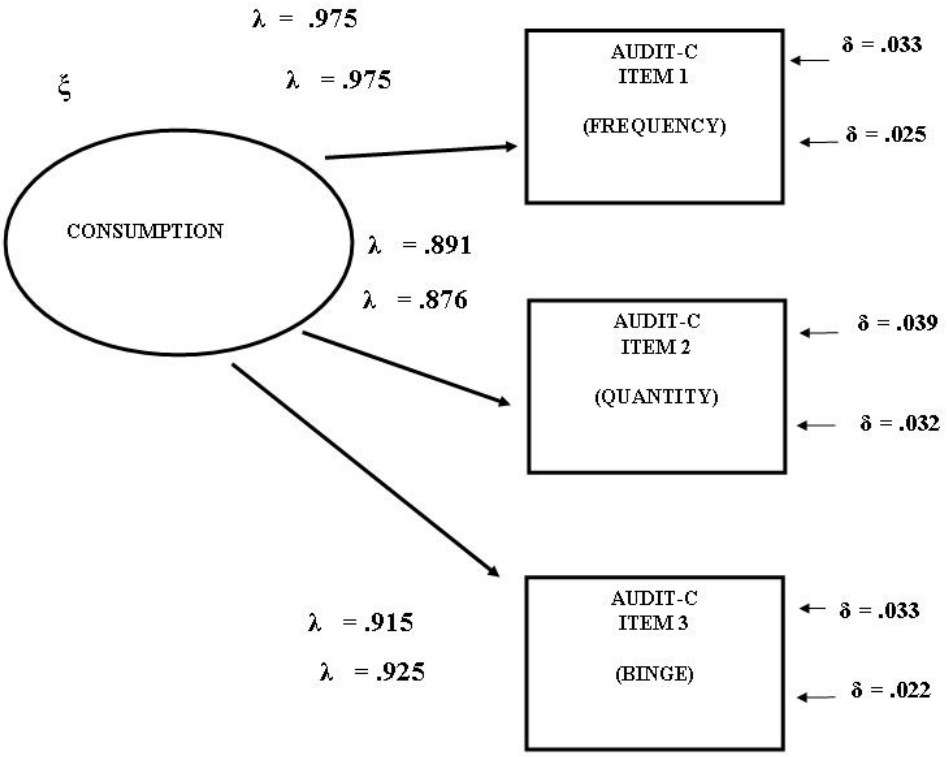
Results of the CFAs by gender revealed that when the factor loadings were constrained across males and females, the resulting model remained nonsignificant X^2 (5, 310) = 4.374, p = .497, suggesting a good fit with the data. Furthermore, the RMSEA value was 0.000 and the WRMR was .440, also suggesting a good fit. Results of the CFAs by race indicated that when the factor loadings were constrained across whites and nonwhites, the resulting model remained WRMR was .440, also suggesting a good fit. Results of the CFAs by race indicated that when the

Table 14: ***Standardized factor loadings for parameter estimates by gender and racial groups***

AUDIT-C item	Males	Females	Whites	Nonwhites
Item 1 (Frequency)	.972	.998	.978	.972
Item 2 (Quantity)	.886	.934	.888	.878
Item 3 (Binge)	.913	.918	.914	.927

factor loadings were constrained across whites and nonwhites, the resulting model remained barely nonsignificant X^2 (4, 310) = 7.889, p = .957, suggesting a marginal fit with the data. Additionally, the RMSEA value was 0.079, essentially meeting the upper limit recommended for indication of a good fit, and the WRMR value was .673, suggesting a good fit. Model modification indices, however, specifically suggested an improved goodness-of-fit if partial measurement invariance was permitted, i.e., if the factor loading for AUDIT item 3 (heavy episodic drinking) was free to vary while the factor loadings for items 1 and 2 remained constrained. Review of the unstandardized factor loadings for whites versus nonwhites also suggested that differences in the contribution of AUDIT-C item 3 by race; $\lambda = .935$ for whites, and $\lambda = 1.425$ for nonwhites. Another CFA was performed where the factor loadings for the first two items were constrained to be equal between the groups and the loading for the third item (episodic heavy drinking) was allowed to vary between the groups. The resulting chi square, RMSEA, and WRMR values suggested that the resulting model indicated a superior fit with the data, X^2 (3, 310) = 1.818, p = .6111; RMSEA = 0.000, WRMR = .340, and no model

modification indices emerged. The final model is depicted in Figure 3, with factor loadings and error terms for whites presented on top in each set, and those for nonwhites presented below.



Note. In each set, factor loadings and error terms for whites are presented on top while those for nonwhites appear below.

Figure 1: ***Final factor-analytic model for the AUDIT-C with partial measurement invariance***

5.5 DISCUSSION

Alcohol use is common among persons with HIV/AIDS; 40-55% of PWHIV acknowledge some degree of alcohol use (Chander, Lau et al., 2006; Galvan et al., 2002; Lucas et al., 2002; Tucker

et al., 2003), and 10-20% of these individuals consume alcohol at hazardous or harmful levels (Arnsten et al., 2002; Braithwaite et al., 2005; Chander, Lau et al., 2006; Conigliaro et al., 2006; Cook et al., 2001; Galvan et al., 2002; Samet et al., 2004; Tucker et al., 2003). Among HIV-infected individuals, alcohol use has been associated with decreased viral suppression and/or immune status (Chander, Lau et al., 2006; Conigliaro, et al., 2003; Samet et al., 2007), decreased survival (Braithwaite et al., 2007), increased rates of comorbid medical illness (Justice et al., 2006), decreased neurocognitive function (Durvasula, Myers, Mason, & Hinkin, 2006), and potential medication interactions and toxicities (Department of Health and Human Services, 2008). Furthermore, alcohol use is generally associated with decreased antiretroviral medication adherence and a dose-response effect appears to exist where greater alcohol consumption is associated with greater likelihood of taking medications off-schedule or missing medication doses/days (Braithwaite et al., 2005; Chander Lau et al., 2006; Samet et al., 2004; Tucker et al., 2003).

Thus, in order to select the most appropriate, patient-centered care and individualized adherence enhancement interventions for PWHIV, HIV/AIDS care providers need accurate and efficient assessment of alcohol risk behavior Conigliaro et al., 2003; Cook et al., 2001; Petry 1999; Samet, Phillips, et al., 2004). This study is one of the few to explore the psychometric properties of the AUDIT-C, and to our knowledge, the only study to do so using a sample of PWHIV; other studies looking at the psychometrics or the performance of the AUDIT-C have used samples of veterans, psychiatric patients, or general primary care patients (Bradley et al., 1998; Bradley et al., 2003; Bradley et al., 2007; Bush et al., 1998; Dawson et al., 2005; Frank et al., 2008; Gordon et al, 2001).

Within the total sample and across subgroups of PWHIV, internal consistency estimates for the AUDIT-C were adequate, falling in between the range of 0.70 to 0.90 which is commonly considered strong without being redundant (Nunnally & Bernstein, 1994). Other internal consistency estimates for the AUDIT-C have not been reported by gender or race and are derived from European and Asian samples; these Cronbach's alphas range from 0.56 to 0.91 (Bergman and Kallmen, 2002; Gomez et al, 2005; Rumpf, Hapke, Meyer, & John, 2002; Tsai, Tsai, Chen, & Liu, 2005). Several studies of the full AUDIT have reported reliabilities by subscale, and describe alpha coefficients ranging from 0.74-0.85 for the consumption subscale, i.e., AUDIT items 1 to 3 (Chung, Colby, Barnett, & Monti, 2002; Maisto, Conigliaro, McNeil, Kraemer, & Kelley, 2000; Shields, Guttmannova, & Caruso, 2004).

Test-retest reliability of the AUDIT-C was adequate for the total sample, males, and whites, but dipped below the commonly accepted standard of 0.70 in females and nonwhites. Two other studies (one of which used a U.S. sample) have also evaluated the AUDIT-C's test-retest reliability. One study using a sample of U.S. male veterans reported a similar range of findings; individual item test-retest reliabilities ranged from 0.65 to 0.85 over 3 months (Bradley et al., 1998). In a Swedish sample drawn from the general population, test-retest reliability for the entire AUDIT-C was 0.93 over a 3 to 4 week period (Bergman & Kallmen, 2002).

The reliability estimates obtained in this study must be interpreted with caution for several reasons. The three month span used in this study is longer than is commonly recommended (3-4 weeks) for test-retest analysis (Carmines & Zeller, 1979); however, the three month time frame is similar to that used by Bradley and colleagues (1998). If the analysis had shown significant differences in scores over time, concerns about maturation effects (participants' drinking patterns changing over time) may be more of a consideration. Also, using

only control subjects for test-retest analyses limited power, and may not have entirely reduced any potential influence of the larger trial on alcohol consumption patterns. Simply through PS participation, individuals assigned to usual care may nonetheless have had additional attention drawn to optimal health behaviors and altered their alcohol consumption or the reporting of their drinking.

The results of the analysis of inconsistent AUDIT-C data suggest that at least for these data, having inconsistent AUDIT-C data cannot actually be well-differentiated on the basis of opiate use/nonuse and conscientiousness score. Thus, it remains unclear why a sizable percentage of PS participants inconsistently responded to the AUDIT-C items. Several other possible explanations exist. First, the possibility exists that individuals with inconsistent AUDIT-C data are different from those with consistent data in some other (unobserved) manner such as health literacy or cognitive function status. Second, although participants completed PS questionnaires at home, at their leisure, the large number of PS questionnaires in the packet at each time point may have contributed to participant fatigue and improper reading of the AUDIT-C questions. Finally, the overall percentage of participants having inconsistent data at one or both time points (13.9%), and the lack of a clear explanation for these inconsistencies suggests that the original wording of AUDIT-C question 2 may inadvertently lend itself to misunderstanding.

The majority of inconsistent AUDIT responses involved situations where individuals acknowledged alcohol use in question 1 but then selected the "0 drinks" option in question 2 which asks about the number of drinks consumed on a typical drinking day. The possibility exists that these individuals misread question 2, which asks, "How many drinks containing alcohol do you have on a typical day when you are drinking?" (Bush et al., 1998) Perhaps some

individuals miss the final clause of the question, and in the presence of an available "0 drinks" response option, interpret the question as "How many drinks do you have on a typical day?"

With respect to the factor structure of the AUDIT-C, even in collapsed form, the first three items of the AUDIT-C are moderately well correlated and load well on a single factor. This reflects consistency with the original intent of the AUDIT and AUDIT-C developers, as well as previous investigations of the factor structure of the AUDIT. The results of the multi-sample CFA by racial group, however, suggest that the assumption of equivalent factor loadings on the AUDIT-C for whites and nonwhites was untenable. Item 3 on the AUDIT-C (episodic heavy drinking) may not be contributing to the consumption construct for whites and nonwhites in the same way.

Previous research has detected differences in alcohol consumption patterns, drinking-related norms, and alcohol-related problems both across and within racial groups (Caetano, Clark, & Tam, 1998; Galvan & Caetano, 2003; Caetano, 2003). Additionally, a large epidemiologic study of binge drinking in U.S. adults reported that the prevalence of binge drinking and the rate of binge drinking episodes (episodes/person/year) were lower for Blacks than for whites, and that both were highest among Hispanics (Naimi et al., 2003). In a related vein, other investigations examining the sensitivity and specificity of the AUDIT-C and the full AUDIT have reported racial differences, but have not gone so far as to recommend different screening thresholds for different racial/ethnic groups (Dawson et al., 2005; Frank et al, 2008; Steinbauer, Cantor, Holzer, & Volk, 1998). These findings, along with the results of this exploratory multi-sample CFA of the AUDIT-C, begin to suggest that perhaps the impact of racial differences has been under-appreciated and requires revisiting.

5.5.1 Limitations

The results of this study require consideration of several limitations. Because alcohol use was not a primary variable of interest in the PS, the amount of variability in alcohol use in the moderately-sized sample was relatively low, thus requiring the collapsing of AUDIT-C response items for CFA. Alcohol use was self-reported; laboratory markers, collateral information, or additional alcohol-related diagnoses were not available. For all analyses in the current study, the AUDIT-C and AUDIT-3 were derived from the full AUDIT in the PS; other investigators have reported that with this approach the AUDIT-C retains high levels of sensitivity and specificity for at-risk drinking and alcohol use disorders (Gordon et al., 2001). However, response bias may nonetheless occur due to the "embeddedness" of these items amidst other questions assessing alcohol use (Dawson et al., 2005; Gordon et al., 2001). Individuals who completely abstain from alcohol use were included in all analyses. While previous studies of alcohol screening instruments have both included (Williams & Vinson, 2001) and excluded "abstainers" from their analyses (Bradley et al., 2007; Canagasaby & Vinson, 2005; Dawson et al., 2005), it must be noted that their inclusion can artificially inflate rates of specificity for the AUDIT-C (Dawson et al., 2005). Finally, while nonwhite individuals were well-represented in the current study, this group consisted primarily of African Americans. Additionally, while the percentage of females was representative of the epidemiology of HIV/AIDS in the region, females nonetheless comprised only one-third of the sample. In turn, some results may not generalize to other nonwhite groups, to individuals identifying as Hispanic/Latino, or to women.

Overall, results require confirmation with larger, prospective samples and samples with greater variability in alcohol use (e.g. perhaps via recruitment through substance abuse treatment

facilities or community agencies). Additionally, future investigations should consider use of a "non-embedded" form of the AUDIT-C; in this study and in others, AUDIT-C and AUDIT-3 responses were extracted from responses to the full AUDIT. While other investigations have shown that in this format, the AUDIT-C does retain high levels of sensitivity and specificity for at-risk drinking and alcohol use disorders (Dawson et al., 2005; Gordon et al., 2001), participant responses may have been different were these items administered independently of the remaining PS AUDIT items and drug-related questions.

5.6 CONCLUSIONS

This study provides preliminary evidence that in general the AUDIT-C is a reliable alcohol screening instrument in persons with HIV/AIDS. The results of the inconsistent AUDIT-C data analysis suggest that researchers who make similar changes to the AUDIT-C or the full AUDIT may encounter problems with the validity of the instrument, particularly in samples where individuals use certain types of illicit drugs. The following ameliorative strategies are proposed for investigators who delete the "skip to" command in AUDIT question 1 and/or add a "0 drinks" option to AUDIT-C question 2. First, it is suggested that investigators who opt to make these changes carefully verify the responses to questions 1 to 3 for consistency. Additionally, various data collection and management programs allow pre-set data validation or conditional formatting parameters which deny or alert the researcher to the entry of invalid responses. Second, researchers making modifications to question 2 might also consider using an interview version of

the AUDIT-C, which would allow clarification of ambiguous or inconsistent responses; the manual for the full AUDIT has an interview version which is identical to the self-report version and which provides simple instructions for the administrator (Babor et al., 2001).

A final consideration is whether or not modifications to AUDIT-C question 2 itself might need to be made when adding a "0 drinks" option, e.g., moving the qualifier to the beginning of the question so that it asks, "*On a typical day when you are drinking*, how many drinks containing alcohol do you have?" However, it remains unclear how these modifications might affect the reliability and validity of the instrument; thus, the previous recommendations may be more advisable. Future methodological or instrumentation investigations of the AUDIT-C or full AUDIT might incorporate a qualitative arm directly querying participants about their interpretation of question 2 when modifications are made, and might further evaluate the psychometric properties of these modified versions.

Finally, the AUDIT-C appears to measure the same alcohol consumption factor across gender and racial subgroups of PWHIV relatively consistently, although some evidence suggests that the understanding of, and response to, the third question on the AUDIT-C may differ across whites and nonwhites. Along with additional methodological investigation, further attention to the cultural equivalence of the AUDIT-C may also be warranted so that other clinicians and researchers can use the AUDIT-C with confidence across patient populations.

6.0 ADDITIONAL RESULTS & DISCUSSION

This chapter provides the results for all analyses conducted as part of Specific Aim #3 and Secondary Aim #1. Discussion by Aim follows each set of results.

6.1 SPECIFIC AIM #3

Specific Aim #3 proposed to compare the effect of the structured and individualized adherence interventions with usual care on the antiretroviral (ART) adherence of persons with HIV/AIDS (PWHIV), and to determine if any effects were moderated by across alcohol screening status (positive/negative on the Alcohol Use Disorders Identification Test—Consumption [AUDIT-C]). In other words, the goal was to detect any statistically significant differences between the changes over time in the adherence of AUDIT-C positive individuals versus the change over time in the adherence of AUDIT-C negative individuals across treatment groups and across time.

6.1.1 Results

The compound symmetry covariance structure provided the best fit with the model (AIC = 4818.820). Significant differences in adherence over time by group and by alcohol screening

status were not detected, i.e., there was no significant three-way interaction between treatment group, time, and alcohol screening status (being AUDIT-C positive/negative), F (2, 239.931) = .049, p = .952. Additionally, two-way interactions between treatment group and time, treatment group and alcohol screening status, and time and alcohol screening status were not appreciated (Table 15). However, main effects for time and alcohol screening status were significant; overall, adherence was significantly lower at Time 2 than at baseline, F (1, 236.287) = 25.595, p = .000, and was significantly lower for AUDIT-C positive individuals than for AUDIT-C negative individuals, F (1, 340.338) = 12.304, p = .001.

The mean dose adherence scores for individuals who were AUDIT-C positive decreased by approximately 13% from baseline to Time 2, i.e., from 70.622 (*SE* = 3.668) to 57.361 (*SE* = 3.989). Mean dose adherence scores for individuals who were AUDIT-C negative were higher overall, but decreased by 10% over the two time points; from 82.499 (*SE* = 2.301) to 72.499 (*SE* = 2.556). A summary of fixed effects appears in Table 16; these relationships are illustrated graphically in Figure 4.

6.1.1.1 Discussion

The finding that dose adherence significantly decreased for all individuals from baseline to Time 2 (3 months) regardless of treatment group (usual care, individualized intervention, structured intervention) was somewhat unexpected, although other researchers using EEM have also reported initial declines in adherence, noting that adherence is also highly variable over time (Howard et al., 2002). It was anticipated that individuals in the intervention groups would demonstrate at least modest improvements in dose adherence. Given that all three groups demonstrated lower adherence, the possibility exists that the effect noted represents a

Table 15: ***Mixed linear model for dose adherence***

Source	Numerator df	Denominator df	F	p
Intercept	1	293.571	1275.963	.000
Treatment group (G)	2	295.432	.965	.382
AUDIT-C status (A)	1	340.338	12.304	.001
Time (T)	1	236.287	25.595	.000
G * A	2	341.292	.666	.514
G * T	2	236.216	.526	.592
A * T	1	240.067	.494	.483
G * A * T	2	239.931	.049	.952

Note. Treatment group = usual care, individualized intervention, or structured intervention; AUDIT-C = Alcohol Use Disorders Identification Test—Consumption (AUDIT-C) positive/negative.

"honeymoon phase" where baseline adherence was artificially inflated due to particular assiduousness or the Hawthorne effect at the start of the trial, then declined to rates more representative of typical medication-taking patterns by the three-month time point. Individuals used the EEM cap for a one-month induction phase where only the last two weeks were used to determine baseline adherence. The first two weeks allowed individuals time to familiarize themselves with cap functioning, and to allow novelty effects to diminish. This time frame may not have been long enough for individuals to return to their typical patterns and rates of medication-taking.

It was not surprising, however, that at both time points AUDIT-C positive individuals

Table 16: ***Summary of estimates of fixed effects for linear mixed models predicting dose adherence***

Parameter	b	SE (b)	p	95% CI	
				LB	UB
Intercept	53.54	7.01	.000	39.77	67.31
Usual Care	1.27	9.34	.892	-17.08	19.61
Individualized	10.19	10.25	.321	-9.96	30.34
Structured	0	0	.	.	.
AUDIT-C negative	12.93	8.31	.120	-3.40	29.26
AUDIT-C positive	0	0	.	.	.
Baseline	16.33	6.80	.017	2.94	29.73
Time 2	0	0	.	.	.

Note. B = parameter estimate; SE B = standard error of the estimate; CI = confidence interval; LB = lower bound; UB = upper bound. AUDIT-C negative and positive represent alcohol screening status at baseline.
Span for baseline to Time 2 was 3 months.

had lower dose adherence than AUDIT-C negative individuals. Although this particular analysis involved change in adherence over time, this finding parallels those of earlier nonparametric analyses where AUDIT-C positive status was associated with significantly lower baseline dose adherence, over-dosing, and under-dosing (Table 5), and earlier regression analyses, where AUDIT-C positive status significantly added to the prediction of baseline dose adherence, *after* controlling for numerous confounding variables and covariates. This finding also parallels the broader ART adherence literature demonstrating that overall, alcohol use tends to negatively

impact adherence (Braithwaite et al., 2005; Chander, Lau et al., 2006; Samet, Horton et al., 2004; Tucker et al., 2003).

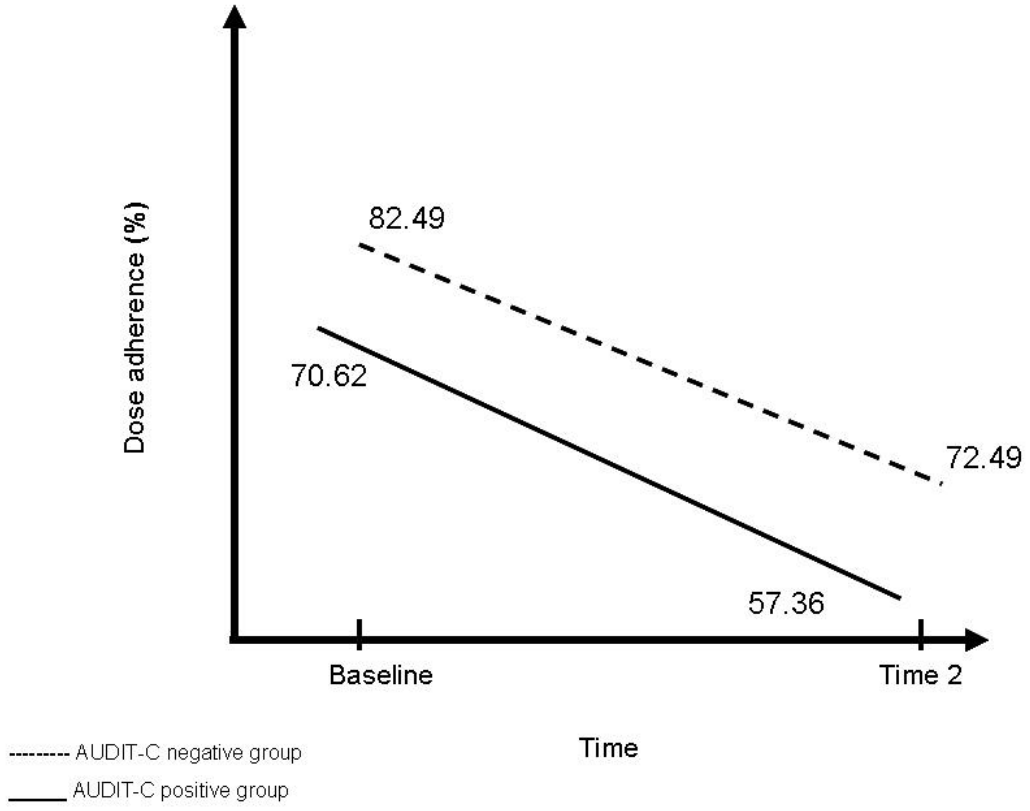


Figure 2: ***Dose adherence over time by alcohol screening group***

6.1.1.2 Limitations

This investigation is only able to comment on the effects of the interventions for the first time point, and for this particular dimension of adherence; the current study did not include additional time points through the 18 month duration of the PS, and did not analyze the effectiveness of the interventions for other types of adherence. It is possible, for example, that while the interventions

may not have impacted overall rates of medication taken versus medication prescribed (dose adherence), it may have had an impact on participants' dosing intervals or on the percentage of entire days where medication was skipped.

The validity of these results may be limited for several reasons. First, the current model is based on baseline AUDIT-C status. AUDIT-C status was treated as a fixed effect but was not permitted to vary over time; baseline status was held constant by carrying forward this status to the second time point. This approach was selected in order to avoid adding additional complexity to the model and because of the percentage of inconsistent or missing AUDIT-C data, particularly at Time 2. However, the assumption that AUDIT-C status did not vary over time is not necessarily valid. Post-hoc analyses of individuals with complete and consistent AUDIT-C and adherence data at both time points (n = 233) revealed that 16.3% of the sample had a change in AUDIT-C status from baseline to Time 2; of these, 7.7% were characterized as AUDIT-C positive at baseline, but AUDIT-C negative at Time 2, and 8.6% were characterized as AUDIT-C negative at baseline, and AUDIT-C positive at Time 2.

Second, missing adherence data was also a problem; a total of 90 participants (27.2% of the sample) had missing dose adherence data at Time 2. Mixed linear models can handle missing data because they fit the model for the response at all time points, but they are valid only when the data can be said to be "missing at random" (MAR), that is, when the probability of having missing data does not depend on the value of the missing data itself, had it been observed (West, Welch & Galecki, 2006). It is possible that the probability of having missing Time 2 adherence data depends not only on factors such as depressive symptoms or age, but on one's rate of baseline adherence. For example, the probability of having missing adherence data at Time 2 might increase as one's rate of baseline adherence decreases. If this is the case, the data would

not be MAR or "ignorable;" models would need to be re-estimated including the missing data mechanism as part of the estimation process itself (Alison, 2001). A preliminary analysis of inconsistent AUDIT-C and missing Time 2 data follows.

6.1.2 Missing data and generalizability of the results

In order to address the generalizability of various findings across the current study, and to determine how individuals with missing adherence data might differ from those with complete data, a series of bivariate and multivariate logistic regression models were run in order to develop a predictive model for having missing Time 2 dose adherence data.

Having Time 1 adherence data from the induction phase was a prerequisite for randomization; only 4 individuals were missing time 1 data. Two of these individuals were removed from their medication by their physicians sometime during the 1-month PS induction phase. One individual did not return the EEM cap at the end of induction. Since these three individuals did not have baseline adherence data, they were never randomized in the PS. One other individual was randomized, but had missing cap data. As the current study used Time 2 data to evaluate the effectiveness of the two adherence interventions over time versus usual care, missing adherence data analysis focused on the second data collection point, Time 2 dose adherence data. As all five types of adherence assessed in this study are derived from the same set of EEM cap data for each participant, the dose adherence variable was selected to represent adherence because it is the most commonly reported form.

A total of 90 participants (27.2% of the sample) had missing dose adherence data at Time 2. In data screening, a dichotomous code was created where individuals having complete

adherence data at Time 2 were coded 0, and where individuals with missing adherence data were coded 1. Baseline values for sociodemographic and other variables potentially associated with missing adherence data were then entered into simple logistic regression models for the prediction of having inconsistent AUDIT-C data. The following variables were individually entered one at a time: gender; age; race (white/nonwhite); years of formal education; the Beck Depression Inventory II (BDI-II) total score; the five subscale scores from the NEO-FFI Five Factor Personality Inventory (Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness), the HIV Self-efficacy Scale total score; dichotomized drug use scores (yes/no) for marijuana, cocaine, crack, heroin, opioids, ecstasy, "poppers," stimulants, hallucinogens, and inhalants. Total AUDIT-C score was also included as a variable using data from the 86% of participants with complete and consistent AUDIT-C data at baseline. Finally, baseline dose adherence scores and treatment group (usual care, individualized intervention, structured intervention) were also individually tested.

In the simple logistic regression models, six (6) variables were associated with having missing Time 2 adherence data: opioid use, heroin use, crack use, baseline dose adherence, treatment group, and Openness score. Opioid users had almost 3.5 times greater odds of having missing adherence data [OR = 3.403, 95% CI (1.532– 7.561), p =.003] compared to non-users. The remaining three variables demonstrated trend relationships ($p < .11$) with having missing adherence data. First, participants who used heroin had almost 3 times greater odds of having missing data [OR = 2.951, 95% CI (1.005 – 8.666), p = .049] compared to non-users, while those who used crack had just over 1.5 times greater odds of having missing data [OR = 1.723, 95% CI (.936 – 3.172), p = .081] compared to those who did not. Second, individuals in each of the two intervention groups had approximately twice the odds of having missing Time 2 adherence data

compared to those in the group receiving usual care; individualized intervention group, [OR = 2.119, 95% CI (1.139 – 3.953), p = .018], and structured intervention group, [OR = 2.001, 95% CI (1.067 – 3.752), p = .030].

Finally, trends were noted where individuals with higher baseline dose adherence scores were slightly less likely to have missing data [OR = .993, 95% CI (.986 – 1.001), p = .073], as were participants with higher Openness scores [OR = .964, 95% CI (.923 – 1.008), p = .107].

Opioid use, heroin use, crack use, baseline adherence score, treatment group, and Openness score were then entered into a multiple logistic regression model for the prediction of having missing Time 2 adherence data. In the final model, only opioid use and treatment group remained significant predictors of missing data. Opioid users had over 3 times the odds of having missing Time 2 adherence data when compared to non-users [OR = 3.041, 95% CI (1.238 – 7.474), p = .015). Those in the two adherence intervention groups again had roughly 2 times greater odds of having missing Time 2 adherence data compared to the usual care group; individualized [OR = 2.179, 95% CI = 1.142 – 4.158), p = .018, structured [OR = 1.980, 95% CI (1.037 – 3.783), p = .039]. Baseline adherence again demonstrated a trend toward the prediction of missing Time 2 data, where those with higher baseline adherence scores had slightly lower odds of having missing data [OR = .993, 95% CI (.985 – 1.001), p = .079].

The Hosmer-Lemeshow test indicated that the model was nonsignificant, indicating a good fit between the model and the data, X^2 (8, n = 334) = 6.772, p = .561. The Nagelkerke R^2 value was .083, indicating that the model explained approximately 8% of the variance in having missing Time 2 adherence data. This model correctly predicted only 73.7% of the cases having missing adherence data, only a slight improvement over a "blind" estimate of the percentage of cases, which was determined to be 73.4%.

6.1.2.1 Discussion

The rate of missing Time 2 data in this study (27.2%) was higher than anticipated by PS investigators, but is not unusual for longitudinal ART trials; general rates of individuals who drop out or who are lost to follow-up are reported to be around 30% (Chesney, Morin & Sherr, 2000). The correct classification of cases in the final model was only 73.7%, suggesting relatively weak differentiation of cases having missing Time 2 adherence data from those having complete adherence data on the basis of opioid use, treatment group, and baseline adherence. However, the significant and near-significant prediction of missing data by treatment group and baseline adherence, even after controlling for drug use and personality, carry substantial implications for earlier repeated measures analyses because they suggest that the "missingness" of Time 2 data may not be "missing at random," i.e., it may be dependent on one's baseline adherence rate and/or adherence intervention group assignment. It is not surprising that individuals with lower adherence might be more likely to have missing data at Time 2; individuals with suboptimal adherence may be more likely to drop out of a long-term adherence trial because of the very same factors contributing to their compromised medication-taking. It is less clear, however, why participants in the intervention groups had twice the odds of having missing data than those in usual care. Perhaps the weekly contact or the nature of the interventions was not appealing to some individuals, namely, those who use substances.

Missing adherence data at Time 2 is attributable to several factors: participant attrition, a missed data collection with return at later time point, cap loss/malfunction, participants' being off medication at Time 2, or participant death. According to PS records, over >90% of missing Time 2 data was due to participant drop out. The bivariate and multivariate associations between various types of drug use (in particular, opioid use) and missing data (primarily due to attrition)

are not surprising given the common difficulty of retaining substance users in clinical trials (Ashery & McAuliffe, 1992; Carroll, 1997). It is noteworthy, however, that in the final model, while opioid use was associated with missing adherence data, heroin use was not. Despite similarities in their physiological mechanisms of action, the context and culture of heroin versus other opioid use can be quite different, resulting in different behavioral manifestations in terms of research participation and attrition. Based on the PS data, we were not able to determine if the approximately 8% of individuals in the sample endorsing opioid use at baseline were misusing prescription drugs, abusing diverted opiates, or enrolled in methadone or buprenorphine maintenance programs. Overall, the results of this study may not generalize well to individuals who use illicit substances.

Howard, Cox, and Saunders (1990) describe a number of attrition prevention strategies in research with substance using populations, including expecting and planning for attrition, using collateral contacts or resources to locate lost subjects, maintaining regular contact with subjects every few weeks, and identifying those who are "at-risk" for attrition and focusing efforts on these individuals. However, not only are these strategies resource-intensive, but as Howard and colleagues point out, they could also feasibly compromise the integrity of treatment protocols by providing ongoing contact, or could compromise original randomization procedures through the additional attention directed towards "at-risk" participants. As drug and alcohol use were not initial variables of interest in the parent study, issues related to the retention of substance-using individuals were not a particular area of focus. Concerns about the effects of such retention strategies on study integrity would have nonetheless been of particular concern to the PS, which tested two adherence interventions over time. All PS did receive modest remuneration with questionnaire and EEM cap return at each time point, and both of the PS interventions involved

weekly contact over 12 weeks. Given the ubiquitousness of polysubstance use among persons who use alcohol and drugs, even future studies focused on alcohol use and ART will likely have to consider the effects of drug use on study attrition, and select ameliorative strategies most appropriate to study aims and characteristics.

6.2 SECONDARY AIM #1

Secondary aim #1 was to explore whether self-efficacy mediated the effects of depressive symptoms, social support, and conscientiousness on dose adherence, and to determine if any meditational relationships were moderated by alcohol screening status (AUDIT-C positive/negative).

6.2.1 Results

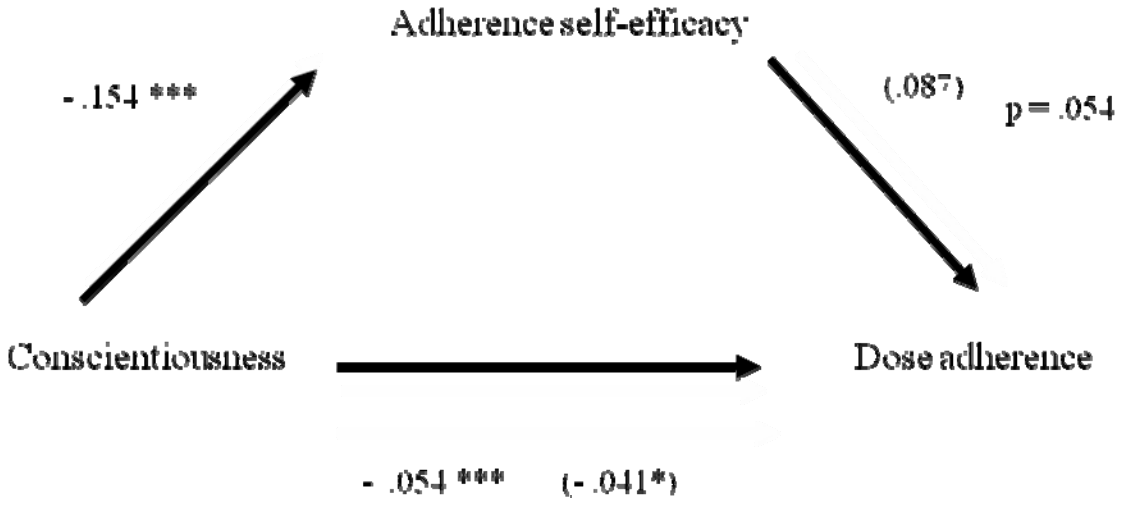
Direct effects between depressive symptoms and social support could not be established; in bivariate correlations and simple linear regression models, BDI-II total score and ISEL total score did not significantly predict baseline dose adherence: depressive symptoms (r_s = -.047, p > .05; F (1, 301) = 1.030, p = .311); social support (r_s = .019, p > .05; F (1, 302) = .091, p = .763). Since the presence of an initial effect to be mediated is a prerequisite for testing mediation (Baron & Kenney, 1986), additional analyses were not performed for these variables.

With respect to conscientiousness, the first two conditions for mediation were met; conscientiousness was a significant predictor of dose adherence, F (1, 299) = 10.80, p = .001,

and of self-efficacy, F (1, 299) = 53.31, p = .000. The third condition required for mediation, however, was not met successfully; there was only a strong, near significant trend for self-efficacy predicting adherence while controlling for conscientiousness, F (2, 298) = 7.324, p = .054. Power was sufficient (.93723) to conduct this analysis. Given the trend toward significance and the fact that the regression coefficient between conscientiousness and adherence did decrease substantially and diminish in significance when controlling for self-efficacy (Figure 1), partial mediation by self-efficacy was at least suggested. Because this aim was exploratory in nature, analysis proceeded using the Sobel test.

Results of the Sobel test also demonstrated a trend towards significance (p=.0635) for partial mediation, reflecting the lack of a previous significant relationship described above and/or the lack of a statistically significant reduction in the size of the regression coefficient. Not surprisingly, these results were further confirmed by bootstrapping estimates (95% Confidence interval -.0317, .0001), where results varied minimally even after increasing the number of booststrap resamples from 3000 to 5000 or 10,000.

Again, because this aim was exploratory and because analyses indicated strong trends, this mediational model was tested for moderation by alcohol use. The interaction between AUDIT-C status and conscientiousness, and the interaction between AUDIT-C status and self-efficacy did not reach significance, (p=.282 and p=.730, respectively), suggesting that any near-significant mediational role for self-efficacy did not differ by alcohol screening status.



Note: The regression coefficient between conscientiousness and dose adherence controlling for adherence self-efficacy is in parentheses. Signs for the coefficients are reversed due to transformations of self-efficacy and dose adherence. *** $p \leq .001$, * $p < .05$

Figure 3: ***Regression coefficients for the relationship between conscientiousness and dose adherence as potentially mediated by adherence self-efficacy***

6.2.2 Discussion

The lack of initial significant relationships between depressive symptoms and ART adherence, and social support and ART adherence, differs from the findings of other investigations. Social support and depression have been consistently associated with ART adherence (Ammassari, et al., 2002; Berger-Greenstein et al., 2007; Catz et al., 2000; Chander, Himelhoch et al., 2006; Vyavaharkar et al., 2007). Numerous path analyses and other modeling studies have revealed the parallel and inverse relationships between social support and negative affect/depressive symptoms, and their subsequent impact on coping, self-efficacy, and in turn, on ART adherence

(Simoni et al., 2006; Vyavaharkar et al., 2007; Weaver et al., 2005). Notably, the mean ISEL total scores observed in this total sample (M = 75.42, SD = 23.27) were considerably lower than those reported elsewhere, and even lower for AUDIT-C positive individuals. Additionally, the mean BDI-II total score was 16.27 (SD = 12.47), falling within the range commonly considered indicative of mild depression (Beck, 1996). Mean scores for AUDIT-C positive individuals, while higher, still fell within this range. These differences suggest that individuals in this sample may have been different from other samples of PWHIV, e.g., these individuals may have been experiencing less depression, may have been engaged in more depression treatment, and/or may have perceived having fewer or less supportive social networks.

The test of mediation by self-efficacy on the relationship between conscientiousness and dose adherence was essentially arrested by failure to meet the third Baron and Kenny (1986) criteria for mediation. This criterion could perhaps have been met through the use of a more precise and compatible measure of self-efficacy. As opposed to the total score for the HIV Self-efficacy Scale, which includes both Self-efficacy Beliefs and Outcome Expectancy, only the Self-efficacy Beliefs subscale score could have been used. The near-significant trend relationship and the reduction in the strength of the conscientiousness-adherence relationship when controlling for self-efficacy suggest however, partial mediation by self-efficacy. This finding is not surprising; broad personality traits related to self-discipline, organization, and goal attainment understandably exert their effects on adherence through self-efficacy for a specific task such as ART dose adherence.

7.0 FINAL DISCUSSION AND CONCLUSIONS

7.1 DISCUSSION

The overall purpose of this study was to further elucidate the impact of alcohol use on the antiretroviral (ART) adherence of persons with HIV/AIDS (PWHIV). This study aimed to determine if positive alcohol screening results on the AUDIT-C added to the prediction of ART adherence over and above sociodemographic, psychosocial and other variables, and to examine the effect of two adherence-enhancement interventions over time, with additional consideration of the potential moderation of these effects by alcohol use. Additionally, the mechanisms through which alcohol affects adherence were explored through the investigation of a potential meditational role for self-efficacy in the relationships between depressive symptoms and adherence, social support and adherence, and the personality factor of conscientiousness and adherence. Finally, this study appraised the psychometric properties and factor structure of the AUDIT-C in a sample of PWHIV in order to provide additional validation for its use as an alcohol screening test in this population.

Overall, these results underscore the prevalence of alcohol use among PWHIV and, like other studies, generally, though somewhat inconsistently confirm the detrimental effects of alcohol on ART adherence. Alcohol use presumably has a negative impact on ART adherence for various reasons. Alcohol may impair cognitive functioning, exacerbate comorbid physical or

mental illness, or compromise interpersonal relationships and social support (Cook, et al., 2001: Hinkin et al., 2006). Additionally, people may forget to take their medication when socializing with alcohol or becoming intoxicated (Cook et al, 2001), or, may actively choose not to take their medications given beliefs about mixing ART and alcohol (Sankar et al, 2007).

HIV care providers are encouraged to screen patients for substance use, and to screen for adherence on an ongoing basis (Stone, 2001). This study used an alcohol screening test (i.e., the AUDIT-C) to categorize alcohol consumption for the prediction of ART adherence, and in so doing, confirmed the findings of others who have detected a significant relationship between alcohol and adherence, particularly those detecting a relationship at low to moderate levels of consumption (Chander et al, 2006; Samet, Horton, et al., 2004; Tucker et al., 2003). The apparent additional prediction of adherence afforded by the AUDIT-C beyond that of sociodemographic, psychosocial, and other variables, draws attention to the intersection of substance use and chronic disease.

The relationship between self-efficacy and medication adherence is well-established. Two findings from this study raise important questions about adherence intervention design, particularly for interventions aiming to improve adherence self-efficacy and for interventions being tested in samples with alcohol use patterns across the spectrum. First, the effectiveness of the adherence interventions was no worse for individuals who screened AUDIT-C positive than for those who screened AUDIT-C negative. Second, the nearly-significant mediational relationship between self-efficacy, conscientiousness, and dose adherence was not moderated by alcohol use. Together, these findings might prompt one to ask if, and exactly how, medication adherence interventions incorporating self-efficacy might need to vary according to the alcohol use status of the individual.

In the broader context of substance abuse, previous authors have drawn attention to the importance of addressing drug and alcohol problems in the context of HIV/AIDS care (Center for Substance Abuse Treatment, 2000; Chander, Himmelhoch et al., 2006; Willenbring, 2005), but findings from the current study suggest the need for additional consideration of the distinction between integrated *care* for alcohol abuse and HIV/AIDS, and integrated *interventions* for alcohol abuse and HIV/AIDS. The efficacy of each approach, as well as the efficacy of one versus the other, remains unclear due to inconsistent research findings. For example, some studies have found no association between ART adherence and engagement in substance abuse treatment (Palepu et al, 2004; Thomas, 2001), while others, namely those involving directly observed therapy (DOT) and/or opiate substitution therapy (methadone, Buprenorphine) for opiate-dependent patients, suggest improved outcomes (Altice, Maru, Bruce, Springer, & Friedland, 2007; Lucas et al., 2007; Macalino et al, 2007; Moatti, 2002). Still others report differences by gender (Turner et al., 2003).

Additionally, only two published studies have been designed to specifically address ART adherence for problem drinkers (Parsons, Golub, et al., 2007; Samet et al., 2005). While both targeted alcohol reduction *and* adherence improvement, their designs differed substantially, as did their findings. Nonetheless, using a timeline follow-back interview method for assessing adherence, Parsons and colleagues (2007) reported significantly greater reductions in alcohol at 3 and 6 months, and improvements in self-reported dose and day adherence at 3 months. Conversely, using the Adult AIDS Clinical Trial Group (AACTG) adherence instruments (Chesney et al., 2000) with electronic event monitoring (EEM) to corroborate self-report, Samet et al. (2005) reported no significant improvements in ART adherence, no reduction in alcohol use, and no improvements in HIV/AIDS clinical markers (Appendix B). In addition to system-

level factors (e.g. financial and human resources) and factors associated with sociodemographic/cultural characteristics of the target population, factors such as the severity of alcohol use, progression of HIV disease, and patient preference/personality may influence the need for an integrated alcohol-reduction/adherence-promotion approach and its potential success. Individualized interventions such as those in the parent study (PS) allow the opportunity for individuals to self-select their health-related goals and plans for achieving them, be they alcohol reduction and/or optimal medication-taking.

However, in this in this sample, having inconsistent AUDIT-C data and having missing Time 2 adherence data were both significantly related to baseline opioid use (but not total AUDIT-C score), and missing Time 2 adherence data was also significantly related to treatment group assignment. In the broader picture, this raises questions about how to best retain substance users in longitudinal ART adherence trials, and/or about the appeal of certain intervention designs and characteristics.

Several authors have recently recommended that ART adherence interventions also incorporate consideration of individual differences in personality (Cruess et al., 2007; O'Clereigh et al, 2007; Ironson et al., 2008; Penedo et al., 2003). Personality is typically considered relatively immutable, so the proposed focus is not on modifying one's personality in order to promote adherence, but instead to enable a person to modify attitudes and behaviors given his or her basic disposition (Ironson et al., 2008). Christensen (2004) describes how individual differences in personality might be accounted for in adherence interventions. For example, individuals high in conscientiousness (who are typically highly self-reliant) may benefit most from adherence interventions which allow for or expect high levels of individual engagement and self-management. The PS interventions addressing problem-solving and habit

training are likely to fit this profile. In a similar fashion, those high in Agreeableness, i.e., those most trusting or deferent to others, may benefit more from group or interpersonally-focused interventions such as peer-to-peer coaching (Christensen, 2004). While the idea that individuals could be matched to adherence interventions based on personality characteristics, dispositions, and response tendencies is appealing, applications beyond intervention selection remain under-developed and under-described. To some extent, this idea also presupposes the availability of multiple intervention options and resources (in which to even refer patients) that may be realistic for only the more resource-endowed facilities and programs.

Post-hoc analyses (change in AUDIT-C status from baseline to Time 2) conducted for the repeated measures analysis challenges the validity of the results from the mixed models. The fact that 16% of individuals in the total sample changed AUDIT-C status over time suggests that analyses examining the effect of the interventions ideally require more complex modeling allowing for time-variant AUDIT-C status (as well as a missing adherence component). The test-retest reliability estimation of the AUDIT-C is unlikely to be invalidated by these changes in AUDIT-C status because it examined the correlation between total AUDIT-C *scores* as opposed to AUDIT-C *status* at the two time points. However, these changes in AUDIT-C status do hint that the 3 month time frame used for the test-retest reliability may in fact be too long for this type of analysis due to people's alteration in drinking patterns or quantity. On the other hand, the AUDIT-C may possess such high sensitivity that even small changes in drinking habits cause one's screening score to change. From a clinical standpoint though, this is encouraging, as the AUDIT-C is meant to identify as many at-risk individuals as possible.

While the AUDIT-C is intended to be particularly easy for individuals to complete and for clinicians and researchers to administer and score, the frequency with which modifications

are reported and the frequency with which this particular sample had inconsistent data when such changes were made suggests that some of its qualities may inadvertently create more challenges than expected. AUDIT-C items of course, mirror those of items 1 to 3 on its parent instrument, the full AUDIT. Certain characteristics of these questions (e.g., containing/not containing a "skip" option in item 1, containing/not containing a "0 drinks" or "none" option in item 2) may appear to be of minor significance, but in this data set, these characteristics did appear to contribute to missing data and/or compromised analyses. From a clinical and research standpoint, the appeal of the AUDIT-3 as a single alcohol screening question again becomes apparent. The appropriateness of the AUDIT-3, however, naturally depends on the intended use of the data, and the AUDIT-3 is not without its own set of potential modifications, e.g., lowering the number of drinks inquired about in the binge question from 6 to $\leq$5 for men and $\leq$4 for women (Bradley et al., 2003).

7.2 LIMITATIONS

The results of this secondary data analysis study require consideration of several limitations. In general, variables were limited to those selected by the PS. Because alcohol use was not an initial primary variable of interest in the PS, the amount of variability in the sample in terms of alcohol use was relatively low. Secondly, because of its purpose as a screening test, the AUDIT-C is designed to be sensitive at the expense of specificity; therefore, the number of individuals who screened positive on the AUDIT-C may have been inflated. The use of gender-specific cut-offs may also have increased the number of false-positive screens in this study. In contrast, however,

the inclusion of nondrinkers in the analysis, i.e., those with total scores of zero on the AUDIT-C, may have artificially increased specificity. Similar considerations apply to the designation of AUDIT-3 positive individuals. Issues related to over-sensitivity of the AUDIT-C are potentially less problematic in the clinical setting, where the aim might be to identify as many individuals with at-risk drinking patterns as possible for further alcohol evaluation or individualized adherence counseling. Finally, AUDIT-C and AUDIT-3 responses were extracted from responses to the full AUDIT. While other investigations have shown that in this format, the AUDIT-C does have high levels of sensitivity and specificity for at-risk drinking and alcohol use disorders (Dawson et al., 2005; Gordon et al., 2001), participant responses may have been different were these items administered independently of the remaining AUDIT items and drug-related questions.

While EEM is often considered the "gold standard" in terms of reliable and objective adherence assessment, and is more highly correlated with viral load and CD4 count, EEM relies on the assumption that cap openings reflect medication ingestion. Additionally, its cost often makes its use prohibitive in research as well as clinical practice. Finally, a self-report measure could be coupled with EEM; the use of multiple assessment modalities is often recommended as the ideal approach for explaining the greatest amount of variance in adherence (Berg & Arnsten, 2006; Pearson et al., 2007).

Several characteristics of the sample underscore the extent to which these findings may be generalized. First, mean adherence rates were relatively high at baseline. For example, dose adherence was near 80% (M = 79.43, SD = 31.63), though similar rates of mean dose adherence (70-80%) have been reported in other ART adherence studies which have used EEM (Golin et al., 2002; Hinkin et al., 2004; Paterson et al., 2000). Additionally, participants were individuals

engaged in care, and highly motivated to participate in a long-term adherence trial. The general rate of alcohol consumption (63.3%) appears to be higher than rates of alcohol use among PWHIV reported previously, which range from 40-55% (Arnsten et al., 2002; Chander, Lau, et al., 2006; Conigliaro et al., 2006; Cook et al., 2001; Galvan et al., 2002; Samet, Horton, et al., 2004; Tucker et al., 2003). Placing the sample's rates of AUDIT-C positive (27.1%) and AUDIT-3 positive (34.2%) individuals in the context of previous research is considerably more challenging due to wide variation in definition and determination of alcohol use patterns across studies. Alcohol consumption may be categorized in terms of quantity/frequency ("moderate," "frequent," "heavy" drinking), risk ("at-risk/risky" drinking) or consequences ("problematic" drinking); in terms of DSM-IV alcohol use disorders e.g., abuse/dependence), or subsumed under the broader variable of "substance abuse." Again, in extant studies, rates of hazardous use and/or binge use generally range from 10-20% (Chander, Lau, et al., 2006; Conigliaro, et al., 2003; Cook et al., 2001), but have been reported as high as 30% (Berg et al., 2004). Given the AUDIT-C's identity as a screening tool, and the fact that it specifically inquires about alcohol use over the past year, the higher rates of hazardous and binge use in this sample are not surprising.

7.3 CONCLUSIONS

In conclusion, secondary data analysis provided the opportunity to assess multiple interrelated aims under the umbrella of alcohol use and medication adherence. These findings carry implications for both clinicians and researchers interested in alcohol use and ART adherence.

Within the context of a systematic alcohol screening program, positive screens on the AUDIT-C may potentially serve as a legitimate cue to action for HIV care providers to inquire further not only about alcohol use, but about possible adherence challenges as well. Additionally, new questions are raised about the extent to which, and the ways in which adherence interventions may or may not need to be modified for different patient drinking statuses. For providers who operate out of a harm reduction model (which prioritizes the pragmatic reduction of problems associated with substance use over complete abstinence from use) (Miller, 2004), this may be encouraging, especially given that some individuals may not be willing or able to simultaneously address abstinence/recovery and adherence enhancement.

The AUDIT-C appears to reliably assess alcohol use in PWHIV. However, without protective strategies in place, researchers who modify the AUDIT-C may risk compromising validity, particularly in samples which include drug users. Further attention to the cultural equivalence of the AUDIT-C across racial/ethnic groups may be warranted.

All of the study findings would be strengthened by confirmation using samples having greater variability in alcohol use. However, the recruitment and retention of individuals who use alcohol is challenging, and appears to be more difficult in the context of polysubstance use. Future investigations should nonetheless consider sampling strategies for improved variability in alcohol consumption, perhaps through recruitment of HIV-positive individuals attending outpatient substance abuse treatment programs. Such a recruitment strategy would allow for greater dimensionalization of alcohol use, e.g., through the comparison of nondrinkers, minimal drinkers, at-risk drinkers, and individuals with alcohol abuse or dependence diagnoses. Additional assessments of alcohol and drug use available through potential partnerships with substance abuse treatment centers would allow additional studies of the AUDIT-C's reliability

and validity. In the future investigators may opt to use a modified AUDIT-3 question as described above, and/or a non-derived format of the AUDIT-C and the AUDIT-3.

Increasing the alcohol use variation in the sample could also feasibly generate opportunities to study the intersection of some patients' need to manage a demanding ART medication regimen within the context of remaining sober and working a recovery program; this intersection has important implications for adherence intervention design and the integration of multiple intervention aims. Wilson, Hutchinson, and Holzemer (2002) have proposed that the process of ART adherence decision-making may need to be conceptualized on a dose-by-dose basis akin to how recovery models conceptualize the daily management of remaining abstinent. This notion remains under-investigated, yet it speaks highly to the complexities and challenges of self-management and behavioral change in the context of multiple health and mental health conditions. Ultimately, the screening and detection of both at-risk drinking and adherence, with even the most reliable and valid of instruments, is of only limited use if the healthcare community is unable to adequately understand and respond to the complexities of managing HIV/AIDS from the patient's lived experience.

APPENDIX A

OVERVIEW OF ALCOHOL USE AND ART ADHERENCE

NON-INTERVENTION STUDIES REPORTING A SIGNIFICANT RELATIONSHIP BETWEEN ALCOHOL USE AND ART ADHERENCE

Study	Sample	Alcohol measures/ operationalization	Adherence measures/ operationalization	Rates of Alcohol/Drug Use	Results	Comments/ limitations
Braithwaite et al., 2005	2352 matched HIV+ and HIV- veterans, multi-center cohort (Veterans Aging Cohort Study—VACS) 94% male ~88% racial minority	Self-report--Time Line Follow Back (TLFB) method for drinking over past 30 days "Abstainers" = no alcohol past 30 days "Nonbinge" = alcohol consumed past 30 days but no day with ≥5 drinks "Binge" = ≥5 drinks/day in past 30 days	Self-report--modified Time Line Follow Back (TLFB) method for medication adherence For main analyses, "nonadherence" = failure to take ≥1 medication dose on given day; for secondary analyses, definition included late doses (> 2 hours after prescribed time)	Alcohol consumption past 30 days: 56.6% None 34.5% Nonbinge 8.9% Binge Average daily consumption 1-3 standard drinks	44% nonadherent (missed or late doses) Temporal effects: For nonbinge and binge drinkers, alcohol consumption on given day associated with decreased adherence on that day as well as the 2 days immediately thereafter. Missed doses most likely to occur on binge days, followed by nonbinge days, and non-drinking days ($p<.0001$ for trend). Dose-response effects: nonbinge and binge drinkers had significantly greater odds of nonadherence (compared to non-drinkers) [Nonbinge, OR=1.6 (1.0-2.6), p =.04; Binge OR= 3.9, CI (2.1-7.4), p <.001]	Did not differentiate between ART and non-ART medications Temporal effect remained significant after removing drug users. Importantly, nonbinge category captures wide range of consumption patterns. Authors acknowledge that temporal definitions preclude those who drink every day (thus perhaps effects of some forms of dependent drinking underestimated).

Cook et al., 2001	219 HIV+ outpatients 72% men 48% MSM 42% racial minority	AUDIT + 2 quantity/frequency questions 3 drinking patterns: "Binge" = ≥5 drinks/sitting for men, ≥6 for women "Heavy"= >16 drinks/month for men, > 12 for women "Hazardous" = AUDIT score ≥8	Self-report "Missed dose" = missed ≥1 dose in past 24 hours "Meds off schedule" = Off schedule unless took meds "all the time" or "nearly all the time" in past week	Alcohol use in past year: 48% None 33% Mild-moderate 19% "Problem drinking" (≥1 of the following: binge drinking (17%), heavy drinking (10%) hazardous drinking (15%))	14% "missed dose(s)" 30% "off schedule" Problem drinkers more likely than nonproblem drinkers to miss doses/take meds off schedule (46% vs. 26%, p =.019) Hazardous and heavy drinking were both significantly associated with taking medications "off schedule" [Hazardous, AOR 2.64, CI (1.07-6.53), p <.05; Heavy, AOR 4.70, CI (1.49-14.84), p <.05] Problem drinkers significantly more likely to report reason for missed doses was drinking *and/or* drug use (26% vs. 3%, p<.001)	Independence of alcohol and drug use? Problem drinkers significantly more likely to be younger and crack/cocaine users (compared to nonproblem drinkers) (p<.01)

Chander, Lau, & Moore, 2006	1433 HIV+ outpatients 64% male, 81% African American	"Hazardous alcohol use" as per NIAAA guidelines† "Moderate alcohol use" = any other drinking	Self-report "Nonadherence"= ≥2 doses missed in past 2 weeks	Overall alcohol consumption: 54.2% None 35.1% Moderate 10.7% Hazardous Overall drug use: 32.6% Alcohol + drug use: 22.2% moderate alcohol only 12.8% Moderate alcohol + drug use 4.8% Hazardous alcohol only 5.9% Hazardous alcohol + drug use	Moderate and Hazardous alcohol use both associated with decreased odds of adherence (compared to No Use) [OR= 0.78, CI (0.64-0.95); and OR= 0.46, CI (0.34-0.63), respectively] Lowest odds of adherence associated with "hazardous alcohol and active drug use" category [AOR=0.32, 95% CI (0.21-0.51]	"Active drug use" = any illicit drug use past 6 months (MJ, heroin, cocaine, etc)
Chesney et al., 2000	75 HIV+ outpatients, multicenter cohort 80% male 68% MSM 31% racial minority	Estimated # drinks/month derived from 2 quantity/frequency questions—how often had drink in past 30 days, # drinks typically consumed	Self –report Adult AIDS Clinical Trials Group (AACTG) Adherence Instruments (2) "Nonadherent" = skipping any of one's medications in the past 2 weeks	Alcohol use past 30 days: 32% None 15% Once/month 19% 2-3x/month 20% 1-2x/week 6% 3-4x/week 6% Nearly every day 2% Daily	Significantly higher Mdn # drinks among nonadherent patients than adherent patients (9 vs. 2, p =.03)	Pilot study for instruments Small sample size

Golin et al., 2002	117 HIV+ outpatients 80% male, 84% racial minority	Yes/no question re: alcohol use in last 30 days	MEMS, pill count, self report (doses missed past 7 days) Composite adherence score derived primarily from MEMS (% doses taken/ doses prescribed over past 4 weeks)	37% reported alcohol use in past 30 days	Average dose adherence 71.3%. Alcohol consumption past 30 days independent predictor of adherence to PI or NNRTI--Drinkers significantly less adherent than nondrinkers (p =.01)	Quantity/frequency information on alcohol consumption not reported Current active drug use also independent predictor of adherence (p =.05)
Halkitis, Parsons, Wolitski & Remien, 2003	456 HIV+ men, multi-center cohort 100% male 94% MSM ~55% racial minority	Self-reported frequency of alcohol use past 3 months; 5 point Likert scale then trichotimized as "no use," "infrequent use," "frequent use"	Self-report # days past 30 days in which $\geq$ 1 dose missed "Nonadherent" = 1 or more days in past 30 days where dose missed	Not reported	51.1% nonadherent Drinking "several times/week" resulted in significantly more missed days than infrequent drinking or abstaining (p =.01 for both) Intoxication in past 3 months and use of alcohol with sex in past 3 months also both sig. associated with nonadherence (p =.01, p=.05, respectively) In MV analysis: Adherence predicted by more frequent use of alcohol, avoidant coping, and sexual communication discomfort [R2= 49.2%;(F (3,48) = 15.48, p .001]	Atypical/unclear operationalization of alcohol use; not clear how many times/week = frequent vs. infrequent 48% endorsed other substance use; crack cocaine significantly associated with nonadherence (p =.04)

Holmes, Bilker, Wang, Chapman, & Gross, 2007	116 HIV+ outpatients 81% male, 66% African American	Not reported, variables simply listed as "no alcohol in past year," "no current drug use"	MEMS for efavirenz only % of prescribed doses taken Dichotomized as "low" and "high" using 95% cutoff	Not reported	No alcohol use in past year was significantly associated with adherence (53% of high adherers had no use vs. 42% of low adherers, p = .01) No drug use significantly associated with adherence (87% of high adherers had no use vs. 78% of low adherers, p = .02) Final logistic regression model included no alcohol & financial worries as predictors of adherence	Secondary data analysis
Howard et al., 2002	161 HIV+ women, multi-center cohort 100% female ~85% racial minority 22% on methadone maintenance	"Alcohol intake $\geq$ 1 day/week" in 6 months prior to study enrollment	MEMS Daily adherence rate, composite adherence rate, monthly adherence rate	Alcohol consumption: 17% "$\geq$ 1 day/week" Other substance use, 6 months prior to study enrollment: 9% IDU 13% crack cocaine	Significantly poorer adherence among women with alcohol use $\geq$1 day/week compared to those who did not (Mean adherence rate 46% vs. 56%, p =.02). In multivariate analysis, alcohol use $\geq$1 day/week remained significantly associated with adherence (p =.04)	Atypical alcohol operationalization; potentially wide range of consumption patterns/quantity, but does suggest that even small amounts of alcohol could adversely impact adherence

Levine et al., 2005	222HIV+ outpatients 80% male 68% African American	SCID; classified as alcohol and/or substance using or dependent if met criteria in past month	MEMS Overall adherence rate: number of openings/number of prescribed doses	21% had substance use disorder	Dose adherence: 44.9% took >90% of doses, 18.9% took 70-90%. Cluster analysis—5 clusters: Very poor adherers (avg 24% adherence), good adherers (>90%), sub-optimal adherers (<80%), moderately poor adherers(~50%), poor weekend adherers (75% weekdays, 57% weekends) Very poor adherers had significantly higher rates of substance use disorders (X^2=17.0, p = .002) (60% vs. rates ranging from 17.6-23.1%) in other groups	No descriptives or separation of alcohol and drug use disorders in "substance use disorder"—primarily drugs? Alcohol? Both?

Lucas, Gebo, Chaisson, & Moore, 2002	695 HIV+ outpatients 62% male, 84% African American	"Substance use"=heroin/ cocaine use *or* heavy alcohol use (≥14 drinks/week) in past 6 months "Nonusers"= no substance use at all surveys "Switchers" = switched substance use status >1 time "Persistent users" = reported substance use at all surveys	Self-reported estimate of #pills missed in past 2 weeks "Nonadherence"= ≥2 doses missed in past 2 weeks	54% Nonusers 29% Switchers 17% Persistent users	Significantly better adherence among nonusers who *remained* nonusers compared to nonusers who *switched* to using ($p<.0001$). Significantly lower adherence among users who *remained* users compared to users who *switched* to non-use ($p<.0001$).	Independence of alcohol/drug use? ("Substance use"=heroin/cocaine use ***or*** heavy alcohol use) Definition of "heavy drinking" unlikely to capture many female problem drinkers, thus underestimating effect of alcohol on adherence among women

Moatti et al., 2000	164 HIV+ French outpatients	Questionnaire including items on alcohol and drug use past 6 months	Self-report "Face-to-face questionnaire" asking "daily # pills of prescribed and effectively taken " in past week, plus "self-administered questionnaire" with additional questions about adherence "Nonadherent" = <80% of doses reported taken *or* acknowledgement that had not been totally adherent"	Not reported	35% nonadherent Risk of nonadherence increased by 20% for each additional 25 glasses (1 glass = 2 units) consumed each month

Murphy, Marelich, Hoffman, & Steers, 2004	115 HIV+ outpatients 76% racial minority	Likert frequency of ≥1 drink in past 3 months "3-day dose adherence" (no missed doses yesterday, day before yesterday, last Saturday) "Past-week dose adherence" (no doses missed past week) "Past-month dose adherence" (took medication "all of the time" or "most of the time" past month)	Self-report 3 dichotomous measures (modified from AACTG instruments)	Frequency of alcohol use (ordinal value): Mean score 2.3, i.e., slightly more often than "once a month or less"	Past-month adherence significantly predicted by alcohol use and social support; those abstaining or less likely to use alcohol were more likely to be adherent ($p < .01$)	Enrollment targeted nonadherent patients (i.e., those missing doses ≥once/week) Gross measure of alcohol use, limited utility of frequency data provided
Palepu, Horton, Tibbetts, Meli, & Samet, 2004	205 HIV+ outpatients 79% male, 66% racial minority Eligibility: "lifetime history of alcohol problems" = ≥ 2 positives on CAGE or clinical assessment by investigators	CAGE for eligibility Self-reported use alcohol/drugs in past 30 days Alcohol Dependence Scale (ADS) for severity of alcohol dependence	30-day self-report "Nonadherent"= less than 95% adherence (pills taken vs. pills prescribed)	Alcohol consumption & drug use past 30 days: 18% alcohol alone 24% alcohol and heroin or cocaine Average daily consumption 6.4 drinks	Use of *drugs or alcohol* in previous 30 days associated with poorer adherence [AOR= 0.17, CI (0.11-0.28)]	Alcohol & drug use combined. Conflation of past/current alcohol abuse and dependence in sampling criterion "lifetime history of alcohol problems"—rate of current problematic alcohol consumption unclear (if only 42 % used alcohol in past 30 days, 58% did not)

Parsons, Rosof, & Mustnaski, 2007	272 HIV+ outpatients with reported alcohol problems Eligibility criteria: score of ≥ 8 on AUDIT 78.3% male 89% racial minority 48% MSM	AUDIT for study inclusion Alcohol consumption via TLFB interview for # standard drinks consumed each day over past 30 days Drinker Inventory of Negative Consequences (DrinC) for negative consequences of alcohol use	TLFB interview re: doses taken and missed over past 2 weeks (converted to %) "Adherence" = ≥95% of doses taken	Not reported	57% nonadherent Number of drinks (p=.002) and Adherence confidence (p =.001) and were significant predictors of adherence; DrinC score and AUDIT score were nonsignificant	Using cut-off score of 8 for AUDIT may only capture heaviest of female drinkers, thus underestimating effect of alcohol on adherence among women.
Samet, Horton, Meli, Freedberg, & Palepu, 2004	267 HIV+ outpatients 81% male 66% racial minority Eligibility criteria "lifetime history of alcohol problems" = ≥ 2 positives on CAGE or clinical assessment by investigators	CAGE for eligibility Quantity/frequency questions + Addiction Severity Index (ASI) for alcohol consumption "At-risk" drinking = NIAAA guidelines[†] "Moderate" drinking = any other drinking	3-day self report, # missed pills "Nonadherent" = less than 100% adherent over previous 3 days	Alcohol consumption: 60% None 24% Moderate 16% At-risk	44% nonadherent Alcohol consumption greatest predictor of 3-day self-reported adherence (p <.0001); abstainers had significantly greater odds of 100% adherence than moderate or at-risk drinkers [Abstainers vs. moderate drinkers, AOR= 3.0, CI (2.0-4.5); Abstainers vs. at-risk drinkers, AOR= 3.6, CI (2.1-6.2)]	Same sample as Palepu, 2004 Independence of alcohol and drug use? Drinkers significantly more likely use heroin (p =0.001) and cocaine (p=<0.0001) in previous 30 days (compared to nondrinkers) Conflation of past/current alcohol abuse /dependence in sampling criterion "lifetime history of alcohol problems"

Tucker et al., 2004	1889 HIV+ persons in HIV Cost and Services Utilization Study (HCSUS) 78% male, 50% racial minority	Self-reported alcohol use past 4 weeks—dichotomous summary measure of "heavy drinking" (≥5 drinks/occasion)	Self-report, # days intentionally/unintentionally missed ART dose and/or took less than prescribed amount in past week + global question re: # days past week took all meds as prescribed "Adherent" = no missed doses and all medications taken as prescribed "all of the time"	6% "heavy drinkers" 5% "heavy drinkers" and drug users"	54% nonadherent For "heavy drinkers," "difficulty getting medication" reported to be significant mediator between substance use and ART nonadherence (p =.04) For those with heavy drinking + drug use, "poor regimen fit with lifestyle" reported to be significant mediator (p <.01)	Drug use predominantly MJ
Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003	1910 HIV+ persons in HIV Cost and Services Utilization Study (HCSUS)	Alcohol consumption past 4 weeks: quantity/ frequency questions, then classified as: No drinking Nonheavy drinking (always <5 drinks/day) Heavy drinking (≥5 drinks on 1-4 occasions) Frequent heavy drinking (≥5 drinks on ≥5 occasions)	3 questions on adherence in past week: # days forgot dose, # days purposely didn't take, # days took less than prescribed + global question on how many days took all meds exactly as prescribed "Adherent"= no missed meds *and* if all meds taken exactly as told "all of the time"	Among those who drink, alcohol use past 4 weeks: 38% Nonheavy drinking 9% Heavy drinking 5% Frequent heavy drinking 28% endorsed drug use (mostly MJ)	54% nonadherent; Alcohol use independently associated with poorer adherence; Multivariate analysis: all 3 levels of consumption significantly increased odds of nonadherence: [Nonheavy, OR=1.5, CI (1.2-2.0), p =.004); Heavy, OR=1.6, CI (1.1-2.3), p = .01; Freq. Heavy, OR=2.3 CI (1.3-4.1), p =.004)]	Dose-response relationship: % adherent persons consistently decreased as alcohol consumption level increased: 52% of Nondrinkers adherent, compared to 43% of Nonheavy drinkers, 39% of Heavy drinkers, 31% of Frequent Heavy drinkers

NON-INTERVENTION STUDIES REPORTING NONSIGNIFICANT OR MIXED FINDINGS ON THE RELATIONSHIP BETWEEN ALCOHOL USE AND ART ADHERENCE

Study	Sample	Alcohol measures/ operationalization	Adherence measures/ operationalization	Rates of Alcohol/Drug Use	Results	Comments/ limitations
Arnsten et al., 2002	85 HIV+ current and former opiate users Bronx HIV Epidemiologic Research on Outcomes (HERO) cohort 95% on MTP 60% male 84% racial minority	# drinks/wk Instrument/ assessment strategy not reported	MEMS over 6 months Adherence rate for each medication = # MEMS openings/ doses prescribed Overall Mean adherence rate based on average of adherence rates for all medications Estimated dose interval adherence = %days $\geq$ 1 dose taken, % days correct dose taken, % days all doses taken within 25% of the correct dosing interval	Average alcohol use during study period: 58% None 16% 0-1drinks/wk 14% 2-5 drinks/wk 12% >5 drinks/wk 31% endorsed an "alcohol or drug coping style," i.e., when under stress or dealing with an upsetting problem, "I use alcohol/drugs to help me get through it," or "I use alcohol or drugs to help me feel better."	Mean overall adherence all meds 53%. Mean dose adherence 38%. Mean interval adherence 23%. Alcohol use several times/wk or every day not significantly associated with poor adherence [Mdn adherence rate 37% vs. 62%, p =.09], however, significant difference in adherence reported between those who did/did not endorse "alcohol or drug coping style" [Mdn adherence 28% vs. 68%, p =.01]	Independence of drug/alcohol use? Sample is opiate users/MTP participants 40% reported active drug use (heroin/cocaine) during study period, active cocaine use significantly associated with poorer adherence [Mdn adherence rate 27% vs. 57%, p =.005] "Coping style" results suggestive of personality differences at play?

Berg, et al., 2004	113 HIV+ outpatients in methadone program 64% male 88% racial minority	"problem alcohol use"= ≥5 drinks/occasion *or* drinking "frequently" (i.e., "several days per week" or "every day") during 6 month study period	Medication event monitors (MEMS); adherence rate for each medication = # cap openings divided by # prescribed doses; average adherence rate = average of all individual medication adherence rates	30% "Problem alcohol use" 27% crack/cocaine use 24% heroin use	No significant differences in median adherence rate between those with/without "problem alcohol use" (40% vs. 69%, p= 0.07), however, significant interaction emerged; women with "problem alcohol use," significantly less adherent than men with "problem alcohol use" (p=.046)	Interaction effect arguably significant
Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000	72 HIV+ outpatients on HAART 87% men 44% racial minority	Frequency of alcohol use past 3 months, 7-point Likert scale from no use to daily use	Self-report # pills missed past 5 days, # days missed doses over past 3 months (7-point Likert scale, never to every day) "Nonadherent" = missed dose ≥ once/week during past 3 months	Not reported	33% missed ≥1 dose in past 5 days 71% missed dose in past 3 months: 4% missed daily, 18% missed weekly, 49% missed monthly Adherence not significantly associated with frequency of alcohol use past 3 months (M frequency score 2.75 vs. 2.85, p = .842)	?Alcohol use dichotomized as yes/no despite 7-point scale? Analytic strategies not clear

Halkitis, Kutnik, & Slater, 2005	300 HIV+ outpatients on HAART 100% male 66.3% racial minority	TLFB interview for use of 10 drugs (including alcohol) 2-week study period	MEMS + self-report via computer-assisted survey for 2 weeks	42.7% of total sample used alcohol during 2-week study period 32.7% of total sample reported use of 1 substance (alcohol or drug) 27% reported use of >1 substance (alcohol or drug) 38% no use of any substance	Via MEMS, 60.7% had adherence ≥95%, and 8.7% had adherence between 90-95%. Via self-report, 67% had adherence ≥ 95% In MEMS and self-report data, adherence not significantly related to alcohol use. Re: substance use, only cocaine use was significantly related to adherence (in both MEMS and self-report data)	During 2-week study period 27% used cocaine/crack 26.3% used MJ
Haubrich et al., 1999	173 HIV+ outpatients, multi-center cohort 92% male 70% MSM 55% racial minority	Frequency of drug *or* alcohol use on 1-item frequency question (7 point scale less than once/week to daily)	Self-reported estimate of % of prescribed medication taken in past 4 weeks, reasons for missing doses Categorized as <80%, 80-95%, 95-99%, 100% "100% adherent"=patients who endorsed >95% adherent *and* who selected "never missed pills" on reasons question	Not reported	No difference in baseline adh among those who drink/use drugs vs. those who don't (38% of alcohol/drug users had 100% adherence at baseline versus 41% of nonusers). However, at 2 months, people using alcohol/drugs were sig. less adherent (>95% adherence) than those who did not (51% vs. 73%, p =.006). At 6 months, the difference was even more significant (47% vs. 84%, p =.003)	Independence of alcohol/drug use? (Single question for both and amounts/types of substances used was not delineated) Complicates interpretation of results; e.g., alcohol and drug use did not impact adherence at baseline, but did at 6 months, when % of users had actually decreased from 32% to 15%)

Hinkin et al., 2004	148 HIV+ outpatients 83% male 83% racial minority Some veterans?	Substance abuse module of SCID for DSM-IV	MEMS over 4 weeks "Good adherers" = ≥95% of prescribed doses taken "Poor adherers" = <95% of prescribed doses taken	Not reported	Mean dose adherence rate 80.7% Current alcohol abuse/dependence diagnosis not significantly associated with adherence [X^2 (1,144) = 0.73, p =.58]	Current drug abuse/dependence was significantly associated with poor adherence [X^2 (1,144) = 4.6, p =.04]
Kleeberger et al., 2001	539 HIV+ men, Multicenter AIDS Cohort Study (MACS) 100% male 16.5% racial minority	Alcohol use: >or ≤14 drinks/week (partial NIAAA categorization) Specific instrument/assessment not reported	Self-report Adaptation of AACTG instruments, assessed 2-, 3- and 4- day adherence with questions related to dose intensity, dose frequency, scheduling, and instructions for overall use "100% adherence" = taking all doses and # pills prescribed for all medications within previous 4 days	Not reported	22.3% nonadherent Consuming > 14 drinks/week not significantly associated with < 100% adherence (OR = 1.57, p =.30)	Extremely stringent definition of adherence

Lazo et al., 2007	Secondary data analysis of 2 large studies: MACS—men and WIHS—women 640 men, 2803 visit-pairs 1304 women, 5972 visit pairs 73% of men were white 15% of women were white	Low alcohol consumption = ≤ drinks/day for men and 0-1 drinks/day for women Moderate-heavy alcohol consumption = 3-4 drinks at least 3times/month OR >5 drinks at a time but less frequently than once/month Binge drinking = > 5 drinks at least once/month for men, >4 at least once/.month for women Drug use for men = self reported MJ, poppers, cocaine/crack, crytstal/meth, speedballs, heroin, XTC Drug use for women = MJ, cocaine/crack, heroin, methamphetamine	Self-report AACTG instrument Adherence dichotomized as 100% or <100% 100% = taking all doses and numbers of pills as prescribed WIHS study looked at past 3 days, MACS looked at past 4 days	Low alcohol consumption: 55% men, 28% of women Heavy: 15% men, 8% women Binge: 7% men, 4% women Use of ≥2 drugs: 27% men, 9% women	All 3 types of drinking behavior were significant, independent predictors of decreasing adherence IN WOMEN ONLY. Binge and low alcohol consumption were inversely related to adherence, and emerged as significant, independent predictors of increasing adherence IN WOMEN ONLY. Drug use was an independent predictor (inversely related) of increasing adherence among men and women.	Secondary data analysis of 2 large studies: MACS—men and WIHS—women. Somewhat complicated alcohol/drug use categories

Paterson et al., 2000	81 HIV+ outpatients, veterans and non-veterans 23% racial minority	"Alcoholism" = ≥2 positive responses on CAGE	MEMS Adherence rate = doses recorded/doses prescribed	13.5% "history of alcoholism" (n=11)	Average dose adherence 74.7%. In univariate analysis, Alcoholism not significantly associated with adherence [RR= 0.28, CI (0.04-1.9, p =.127] In multivariate analysis, absence of alcoholism not associated with adherence: [OR=5.8, CI (0.6-57.8), p =.13]	Adequate power? Risk of Type II error given that only 11 individuals with "alcoholism"
Spire et al, 2004	445 HIV+ French outpatients on HAART (AROCO-ANRS/EP11 Study) 78% male	10 questions on alcohol/drug use over past 4 weeks ≤1 unit/day vs. >1 unit/day	Self report 4 day recall, # pills taken daily + global question re: having taken doses "totally," or "partially," or if they had "interrupted treatment." "Adherent" if doses taken past 4 days = doses prescribed *and* if declared "totally" followed regimen	At baseline, 26% consumed > 1 unit/day 74% consumed ≤1 unit/day	26.7% nonadherent Baseline alcohol consumption of >1 unit/day of alcohol not significantly associated with adherence at month 4 (67.2% of those consuming >1 unit/day were adherent vs. 75.4% of those consuming ≤1 unit/day, p =.09). However, --increasing one's consumption level from ≤1 unit/day to >1 unit/day was associated with greater odds of adherence at month 4 [AOR 2.24, CI (1.35-3.71)]	

Waldrop-Valverde et al, 2006	57 HIV+ outpatients 77% male 96% racial minority	Questionnaire based on SCID for DSM-IV, substance abuse module—included items on frequency, duration, and time since last use Participants categorized as yes/no re: "use of alcohol in past week"	Self-reported 1-day adherence "Adherence" = 100% 1-day adherence	50% reported drug/alcohol use in past week Average length of alcohol use: 19 yrs	42% nonadherent Alcohol use and drug use in past week not significantly related to adherence in any of the 3 logistic regression models tested	Sample with longstanding substance abuse issues: Average length of use: heroin 13 yrs cocaine 14 yrs MJ 19 yrs

APPENDIX B

ADHERENCE INTERVENTIONS FOR HIV-INFECTED PERSONS WHO USE ALCOHOL

Study	Samet et al, 2005	Parsons, Golub, Rosof, & Holder, 2007
Theoretical basis	Readiness for change (Transtheoretical Model--Prochaska & DiClemente, Miller & Rollnick, etc.)	Information-Motivation-Behavior (IMB), Motivational Interviewing (MI), Cognitive-Behavioral Skills Training
Design	Randomized controlled trial, intervention vs. usual care	Randomized controlled trial, intervention vs. education
Aims	Improve ART adherence, reduce alcohol consumption, improve clinical outcomes (CD4, viral load)	Improve ART adherence, reduce alcohol consumption, improve clinical outcomes (CD4, viral load)

Sample characteristics	n=151 HIV-infected persons with "current or lifetime history of alcohol abuse or dependence" (based on ≥2+ responses on CAGE questionnaire, or, clinical diagnosis made by 1 study investigator) ; ~80% male	n=143 HIV-infected persons identified as "hazardous drinkers" (>16 drinks/week for men, >12 drinks/week for women); ~80% male, 94% racial/ethnic minority, Mean age 43.6
Alcohol use measures	Initial inclusion criteria as described above. Consumption measured by Addiction Severity Index (ASI) + frequency/quantity questions	Initial inclusion criteria by AUDIT score ≥8; followed by criteria above. Standard drinks consumed measured by Timeline Follow-back Interview (TLFB) for past 14 days
Adherence measures	Self-report (ACTG scale) corroborated by MEMS at certain timepoints dose adherence dichotomous + continuous over past 30 days, past 3 days	Self-report (TLFB interview) dose and day adherence % dose adherence past 14 days, % day adherence past 14 days
Intervention duration/intensity/ components	4 sessions, 15-60 minutes each Alcohol and substance use (readiness to change) Reminder device (watch with alarm)	8 sessions, 60 minutes each (applies to both adherence intervention and educational intervention)

	Review of ART efficacy Tailoring medication-taking to personal circumstances	Adherence intervention: Alcohol use (MI) Tailored skills-building and self-assessment/monitoring modules (e.g., side effects, alcohol triggers/refusal strategies, social support) Education: Didactic, videotapes, discussion on HIV, ART, and alcohol
Results	No significant improvements in ART adherence, reduction in alcohol use, or improvements in clinical markers	From baseline to 3 months, both groups had significant ↑ in % dose and % day adherence. Adherence intervention group had significantly *greater improvements* in % dose adherence and % day adherence compared to education group. Alcohol consumption significantly ↓ in both groups at 3 month and 6 month time points.

Limitations	Lower than anticipated enrollment limited statistical power ~25% of sample received partial intervention or no intervention High rates of adherence at baseline; may → ceiling effect	Low statistical power at 6 month time point due to attrition. Adherence effects not sustained at 6 month time period (may require booster sessions)
Critique	Conclusions re: need for directly observed therapy (DOT) in this population are somewhat premature given significant methodological limitations of the study and intervention characteristics. Intervention seems intended to be clinically feasible in terms of duration/intensity, and combines information needs (ART) and readiness to change (substance use), with practical, life-relevant dimensions (reminder device, tailoring to circumstances). The Simoni (2006) meta-analysis also reported a nonsignificant trend where intervention effect sizes tended to be larger in studies that included "didactic information on HAART" and those including "interactive discussion of cognitions, motivations, and expectations regarding adherence" (p. S31). The brief	Intervention may be challenging to replicate in clinical setting. While this intervention appeared to be more theoretically-driven and of greater intensity and duration that that described by Samet (2005), a meta-analysis by Amico (2006) reported that articulation of theoretical basis and intensity/duration of intervention were not related to the magnitude of effect sizes. However, characteristics of the intervention and the study's low percentage of individuals adherent at baseline and intervention characteristics may partially explain the intervention's apparent effectiveness. The meta-analysis by Amico (2006) also reported that intervention studies targeting persons with low adherence at baseline showed larger effect sizes than those that did not enroll in this

	intervention description provided by Samet (2005) suggests that didactic and motivation components were incorporated into the intervention, however, limited information about the theoretical underpinnings and specific content of the intervention leave questions about the role of intervention design in the study's lack of significant findings.	manner. While the Parsons study did not target low adherers during enrollment, baseline adherence was 38% for the sample. Additionally, the study's targeting of persons with alcohol problems may have served as a proxy for this phenomenon. The Simoni (2006) meta-analysis also reported a nonsignificant trend where intervention effect sizes tended to be larger in studies that included "interactive discussion of cognitions, motivations, and expectations regarding adherence" (p. S31); the intervention description provided by Parsons (2007) appears consistent with this characteristic.
	Criteria of "current or lifetime alcohol abuse/dependence" may have impacted the effect of the intervention. Other studies have demonstrated that adherence is different when one considers past vs. current use and/or different levels/patterns of alcohol consumption. Information about current alcohol consumption patterns of the sample or what % of persons fell into each category/permutation was not reported.	
	Lack of intervention efficacy does not appear to be related to depression, concurrent drug use, homelessness, disease status, pill burden—no significant differences between groups	Adherence intervention did not result in greater reductions in alcohol use than the education module—may be due social desirability issues around reporting alcohol reduction vs. adherence improvements or that information alone is effective for alcohol-related behavior change, whereas adherence behavior change
	Low % of women in sample, but meta-analyses by Simoni (2006)	

	and Amico (2006) both showed that gender did not appear to be related to intervention effect size.	requires additional components (authors' interpretations). Low % of women in sample, but meta-analyses by Simoni (2006) and Amico (2006) both showed that gender did not appear to be related to intervention effect size. No info on those with concurrent drug use

APPENDIX C

INSTITUTIONAL REVIEW BOARD APPROVAL

University of Pittsburgh

Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

TO: LAUREN BROYLES
FROM: SUE BEERS PHD, Vice Chair
DATE: 3/13/2008
IRB#: PRO08030117
SUBJECT: Alcohol Use, HIV Infection, and Adherence

The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section 45 CFR 46.101(b)(4) existing data.

Please note the following information:

- If any modifications are made to this project, please contact the IRB Office to ensure it continues to meet the exempt category.
- Upon completion of your project, be sure to finalize the project by submitting a termination request.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

OSIRIS Request for Determination of Exempt Status, or No Human Subjects Designation:
Existing Data or Research Records

Title of Study: Alcohol Use, HIV Infection, and Adherence
Principal Investigator: Last name: **Broyles** First name: **Lauren**
NOTE: This form is not applicable for study of Medical Records
A. Will any information from this project be submitted to the FDA or held for inspection by the FDA? No ☒ Yes ☐
B. Check type(s) of measures to be used: ☐ Publicly available information; ☒ Research Records (Describe Source): "Adherence to Protease Inhibitors," R01NR04749 ; Other data (Describe): .
C. How will information be recorded? (check all that apply) 1. ☐ Information is publically available and will be recorded by or provided to investigators to include subject identifiers; 2. ☐ Information (without identifiers or linkage codes) will be provided to this investigator by other researchers who are independent of this project; 3. ☐ Information is recorded anonymously (no identifiers or linkage codes) by the investigator; 4. ☐ An independent honest broker, not associated with this research study, will de-identify data prior to providing it to the investigator and will not assign linkage codes; 5. ☒ An independent honest broker, not associated with this research study, will de-identify data prior to providing it to the investigator and will assign linkage codes; but the investigator will not have access to the linkage codes a. ☒ The following person or group, who is independent of the research team, has agreed to serve as the honest broker: Blair Powell; documentation of that agreement is attached. b. ☐ Information electronically de-identified by a computerized system over which research team has no access (e.g., Pitt De-ID program; other program (name):
D. Is a copy of data extraction form or a list of variables attached or uploaded? No ☐ Yes ☒. **If no, why not?**
E. Are all data currently in existence? No ☐ Yes ☒. **If no, please explain:**

IRB Protocol

1. **Study Aims**

   (a) **What is this research intended to accomplish**? The purpose of this study is to further elucidate the impact of alcohol on antiretroviral (ART) adherence among persons with HIV/AIDS (PWHIV). Primary aims are to: 1) characterize the sample, particularly any joint effects of alcohol consumption, gender, and race; 2) determine the extent to which alcohol consumption predicts baseline ART adherence; and 3) compare the effect of structured and individualized adherence interventions with usual care on the ART adherence of PWHIV who consume alcohol. Secondary aims are to 4) explore whether self-efficacy mediates the effects of depressive symptoms, personality characteristics, and social support on the ART adherence of PWHIV who consume alcohol, and 5) to evaluate selected psychometric properties of the Alcohol Use Disorders Identification Test-Consumption Scale (AUDIT-C).

2. **Background and Significance**

(a) **What observations or prior scientific findings serve as the basis for this study**? Although approximately 40-55% of PWHIV acknowledge various degrees of alcohol use (Chander, Lau, & Moore, 2006; Galvan et al., 2002; Lucas, Gebo, Chaisson, & Moore, 2002; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003), understanding the influence of alcohol use on adherence continues to be limited (Chander, Himelhoch, & Moore, 2006). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has recently identified the need for increased research on improving medication adherence among HIV+ individuals who use and misuse alcohol, including the development of explanatory models that "increase understanding of the multidimensionality of the relationship between alcohol use and "abuse" and adherence to HIV therapeutic regimens. . ." (Bryant, 2006, p. 1492), i.e., models which include the variety of individual, social, and contextual factors affecting alcohol use and health behavior.

(b) **Why is it important to conduct this research**?
Suboptimal ART adherence contributes to decreased viral suppression and drug resistance, and subsequently, the potential for higher healthcare costs and the proliferation of resistant strains of HIV in the community. Relatively few ART adherence investigations have focused on the impact of alcohol use, in particular, its impact independent from that of drug use. Studies exploring the relationship between alcohol and ART adherence report inconsistent findings, and often require careful evaluation in light of various methodological limitations, e.g., inconsistent or ambiguous definitions and measurement of "alcohol use" and "adherence," and the exclusive use of self–report data for assessment of adherence patterns (Chander, Himelhoch et al., 2006; Cook et al., 2001). Finally, a limited number of studies have heretofore attempted to elucidate the role of various psychological and environmental factors in the alcohol-adherence relationship such as self-efficacy, depressive symptoms, personality, and social support (Braithwaite et al., 2005; Parsons, Rosof, & Mustanski, 2007; Tucker et al., 2004), and only a few studies have described tailored adherence interventions aimed at PWHIV who drink (Parsons, Golub, Rosof, & Holder, 2007; Samet et al., 2005).

Important questions remain about the extent to which various levels of alcohol consumption interfere with ART adherence, the mechanisms through which this interference might occur, and the effectiveness of ART adherence-enhancing interventions among PWHIV who consume alcohol. Given the prevalence of alcohol use, the significant personal and public health implications of suboptimal ART adherence, and the fact that alcohol use is a modifiable behavior, a more comprehensive understanding of the interplay between alcohol use, adherence, and various personal, behavioral, and environmental factors is warranted. Findings from this study will support the development of individualized, patient-centered ART adherence strategies.

3. **Records to be studied**

(a) **What records will be accessed**? The "parent study" for this Secondary Data Analysis is R01 NR04749, "Adherence to Protease Inhibitors," Principal Investigator, Judith Erlen, PhD, IRB#970958. Specifically, data from Phase II of the parent study (2003-2008) will be used.

(b) **Describe PI's right to access these records.** The PI for the Secondary Data Analysis, Lauren Broyles, is a doctoral student at the School of Nursing. The parent study PI, Dr.

Erlen, serves as academic advisor to Ms. Broyles and has given permission for her to access these records.

(c) **Unless data are publically available, investigators cannot record subject identifiers with data. Are personal identifiers associated with the original data?**
☐ **No;** ☒ **Yes**

(i) **If records currently have identifiers, describe how they will be de-identified prior to being provided to the investigators** (if applicable).

(ii) **If linkage codes will be assigned to the data provided to the investigators, identify person or group responsible (e.g., independent "honest broker"; original researcher).** Total de-identification of the data will be performed by an "honest broker" (Mr. Blair Powell, Data Manager with the Center for Research in Chronic Disorders at the School of Nursing) prior to analysis and individuals will be assigned new study identification numbers (i.e., codes) for the SDA. The Principal Investigator and collaborating members of the dissertation committee will be denied access to any linkages between PS data, PS study identification numbers, and SDA identification numbers. Therefore, all investigators will be unable to readily ascertain the identity of the individuals to whom the SDA-coded information pertains, and the linking of information to any particular participant will not be possible.

4. **Methods**

(a) **Describe or list variables that will be extracted from records. Sociodemographic data** (e.g., gender, race/ethnicity, marital/educational status, income) will be extracted from a comprehensive standard instrument developed by the Center for Research in Chronic Disorders at the School of Nursing. **Disease profile parameters** (CD4 count, detectable/undetectable HIV RNA) will be obtained through the PS-designed Medical Record Review. Participant responses from items 1-3 of the Alcohol Use Disorders Identification Test, i.e., the AUDIT-C (Bush, 1998), will be used to describe and categorize the independent variable **alcohol use. Antiretroviral adherence** was measured by electronic event monitoring (EEM), which treats adherence as a continuous variable. More specifically, **dose adherence** (% medication administrations), **day adherence** (% of days with correct # of pills taken), **days over-dosing** (% of days with more than prescribed number of administrations taken), **days under-dosing** (% of days with less than prescribed number of administrations taken), and **days with null dosing** (% of days with no medication administrations at all) will be extracted/calculated. Adherence will also be assessed with 2 self-report instruments, the ACTG Adherence Questionnaire and the Electronic Event Monitoring System Questionnaire (NIAID AIDS Clinical Trials Group). **Self-efficacy** for ART adherence will be extracted from the HIV-Self-efficacy Scale (HIV-SES) developed by the parent study. **Depressive symptoms** will be extracted from the Beck Depression Inventory-II (BDI-II) (Beck, 1996). **Personality characteristics** will be extracted from the NEO Five Factory Inventory (Costa & McCrae, 1992). **Social support** data will be obtained from the Interpersonal Support Evaluation List (ISEL) (Cohen, 1985).

(b) **Where will study be conducted, and who will record data (without identifiers)**?

The proposed secondary data analysis will be conducted at the University of Pittsburgh School of Nursing. All PS data were collected from 1999-2008, and exist on a secure server within the Center for Research in Chronic Disorders at the School of Nursing. Using SPSS, version 15.0 (SPSS Inc., 1989-2004), data sets by measure will be extracted from the PS master database/server, and merged into a common file for analysis by the PS data manager. Again, Mr. Blair Powell, Data Manager with the Center for Chronic Disorders at the School of Nursing, will serve as the honest broker and will assign new study identification umbers (i.e., codes) for the secondary data analysis.

5. **Analysis**

(a) **How will results be analyzed to determine that study aims have been met**? For **Primary aim #1** (characterizing the sample of PWHIV, with special attention to any joint effects of alcohol consumption, gender, and race, descriptive statistics (e.g., measures of central tendency, dispersion, distribution, correlations) will be generated. With respect to **Primary aim #2** (determining the extent to which alcohol consumption categories predict baseline ART adherence) multiple linear regression will be used to compare the *baseline* (T1) adherence across levels of alcohol use. For the purposes of **Primary aim #3** (comparing the effect of an adherence intervention with usual care on the ART adherence of PWHIV who consume alcohol), repeated measures analysis (e.g. covariance pattern models using mixed modeling methods) will be used in order to determine if alcohol use impacts the effect of the adherence intervention (i.e., interaction) on adherence over time--T1 to T2, i.e., baseline to 12 weeks follow-up. With respect to **Secondary (exploratory) aim #1** (exploring whether self-efficacy mediates the effects of depressive symptoms, personality characteristics, and social support on the ART adherence of PWHIV who consume alcohol), multigroup path analysis will be used to identify the role of ART adherence self-efficacy as a potential mediator of the relationship between adherence and depressive symptoms, personality characteristics, and social support. With respect to **Secondary (exploratory) aim #2** (evaluating various psychometric properties of the AUDIT-C using a sample of PWHIV), reliability estimations will include internal consistency and test-retest reliability. Internal consistency of the AUDIT-C will be estimated using Cronbach's alpha. To assess test-retest reliability of the AUDIT-C, data from the T_1 (baseline) and T_2 (post-intervention, i.e., 3 months) time points will be used to conduct paired t-tests (assuming normality). Multi-sample confirmatory factor analysis (CFA) (Chi & Duda, 1995) will be used to examine the hypothesized single factor structure of the AUDIT-C, first using the entire sample of PWHIV, then using cross-validation samples based on gender (male-female) and race/ethnicity (White-NonWhite).

6. **Summarize the qualifications and experience of the Principal Investigator that are relevant to the conduct this research study:** Ms. Broyles is a doctoral student at the School of Nursing, and a predoctoral fellow funded by the NIH (National Institute of Nursing Research, F31 NR008822). She has successfully completed all coursework in the PhD program and has completed Overview and Comprehensive Exams with dissertation committee approval. Ms. Broyles' clinical nursing background includes acute care of persons with HIV/AIDS and consulting work on the Substance Abuse Consultation-Liaison Service at the University of MD Medical System. She has several first-authored publications related to substance use, persons with HIV, and adherence, and has secured

additional external funding to investigate substance use and psychiatric conditions among hospitalized patients.

Dr. Judith Erlen, PI for the parent study, serves as Ms. Broyles' academic advisor and formal mentor for the aforementioned predoctoral fellowship. Now near completion, the parent study for the proposed SDA has focused on understanding and improving adherence to antiretroviral treatment through the testing of a habit-training and problem-solving intervention. Dr. Erlen is well-integrated as a faculty member of the School of Nursing; she serves as Professor, Associate Director for the Center for Research in Chronic Disorders, and as the Doctoral Program Coordinator. Her program of research has focused on adherence in chronic illness, including HIV/AIDS. She serves as a collaborator on the Adult AIDS Clinical Trials Group (AACTG), and is co-PI with Dean Dunbar-Jacob on "Improving Medication Adherence in Comorbid Conditions." She has served as a consultant on "Symptom Management with HIV Infected Older Adults," and "Adherence to Antiretroviral Therapy in HIV-positive Women." Dr. Erlen has published extensively on adherence to treatment regimens in chronic disorders, and previously on alcohol and ART adherence (Cook et al, 2001). Finally, Dr. Erlen has mentored five students who have received predoctoral fellowships or other funding, as well as several international postdoctoral students.

7. **Additional Information, Clarification, or Comments for the IRB Reviewer**:

a) Based on the initial funding submission to NIH (National Institute of Nursing Research, F31 NR008822), approval under ***45 CFR 46.101(b)(4)*** is requested for this application.

b) Please see attachments for variables list and references.

*****

CERTIFICATION OF INVESTIGATOR RESPONSIBILITIES

By submitting this form to the IRB via OSIRIS, I agree/certify that:

1. I am cognizant of, and will comply with, current federal regulations and IRB requirements governing human subject research.

2. I have reviewed this protocol submission in its entirety and that I am fully aware of, and in agreement with, all submitted statements.

3. I will conduct this research study in strict accordance with all submitted statements.

4. I will ensure that all co-investigators, other personnel assisting in the conduct of this research study, and members of the Honest Broker System have been provided a copy of the entire current version of the research protocol.

5. I will request and obtain IRB approval of <u>any proposed modification to the research protocol that may affect its designation as an exempt or 'no human subjects' application</u> prior to implementing such modification.

6. I will ensure that all members of the research team have satisfactorily completed the Research Integrity (module 1) and Human Subjects Research (module 2a or 2b) web-based training programs.

7. Neither I, nor any member of my research team, will intervene or interact with the patients whose medical records are being studied in this research project.

8. Neither I nor members of my research team will have access to patient identifiable information should linkage codes be used by an honest broker.

9. I will ensure that if linkage codes *are* recorded with these data, the person or group responsible for recording linkage codes is completely independent of this project and that those individuals have been approved by the IRB to serve as honest brokers.

10. I will not submit this application to the IRB until the Honest Broker has reviewed this protocol and has agreed to provide me with either a HIPAA safe-harbor data set, or a limited data set, as described above in this application.

11. I will not begin conducting analyses until the status of this application has been determined by the IRB and I have been informed in writing.

12. I will respond promptly to all requests for information or materials solicited by the IRB.

13. I will maintain adequate, current, and accurate records of research data.

14. I will not knowingly include data from prisoners.

End of Application (Form: EXEXIST 041707) **Please Save File and Upload Into OSIRIS**

Honest Broker MUST complete and sign Assurance Form (next page); one copy should be retained by Honest Broker, and one copy should be uploaded into OSIRIS

Independent "Honest Broker" Assurance

By signing below, I agree / certify that:

1. I have reviewed this project with the Principal Investigator and agree to de-identify and, if applicable, to maintain linkage code information for data (including specimens) that will subsequently be accessed by the research team.

2. I will, under no circumstance, provide the PI or any member of the research team with information that would permit the identification of research subjects.

3. I will not intervene or interact with identified human subjects during the conduct of this research project.

4. I will maintain complete confidentiality of research subjects' private information.

Title of Study: Alcohol Use, HIV Infection, and Adherence
Principal Investigator: Lauren Matukaitis Broyles, Doctoral student
Judith Erlen, PhD, Advisor/mentor

Name: Blair Powell	Signature:	Date: 3-4-08
Position: DATA MANAGER	e-mail: blair1@pitt.edu	Phone: 412-624-0963
Additional optional comments of Honest Broker:		
Name of Honest Broker System or Process:	UPMC/IRB Honest Broker Approval Number:	

Please scan or digitize (if needed) file – to include signature! – and upload into OSIRIS

BIBLIOGRAPHY

Alison, P. D. (2001). *Missing data*. Thousand Oaks: CA, Sage Publications.

Altice, F. L., Maru, D. S., Bruce, R., Springer, S., & Friedland, G. (2007). Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: A prospective, randomized, controlled trial. *Clinical Infectious Diseases, 45*, 770-778.

Altice, F. L., Mezger, J. A., Hodges, J., Bruce, R. D., Marinovich, A., Walton, M., et al. (2004). Developing a directly administered antiretroviral therapy intervention for HIV-infected drug users: Implications for program replication. *Clinical Infectious Diseases, 38 Suppl 5*, S376-387.

Amico, K. R., Harman, J. J., & Johnson, B. T. (2006). Efficacy of antiretroviral therapy adherence interventions: A research synthesis of trials, 1996 to 2004. *Journal of Acquired Immune Deficiency Syndromes, 41*(3), 285-297.

Ammassari, A., Trotta, M. P., Murri, R., Castelli, F., Narciso, P., Noto, P., et al., (2002). Correlates and predictors of adherence to highly active antiretroviral therapy: Overview of published literature. *Journal of Acquired Immune Deficiency Syndromes, 31*(Suppl3), S123-127.

Arnsten, J. H., Demas, P. A., Grant, R. W., Gourevitch, M. N., Farzadegan, H., Howard, A. A.,

et al. (2002). Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *Journal of General Internal Medicine, 17*(5), 377-381.

Ashery, R., & McAuliffe, WE. (1992). Implementation issues and techniques in randomized trials of outpatient psychosocial treatments for drug abusers: Recruitment of subjects. *American Journal of Drug & Alcohol Abuse, 18*(3), 305-329.

Au, D. H., Kivlahan, D. R., Bryson, C.L., Blough, D., Bradley, K. A. (2007). Alcohol screening scores and risk of hospitalizations for GI conditions in men. *Alcoholism: Clinical and Experimental Research, 31*(3), 443-451.

Babor, T. F., Higgins-Biddle, J.C., Saunders, J.B., Monteiro, M.G. (2001). *Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care* (2nd ed.). Geneva: World Health Organization.

Bandura, A. (1986). *Social foundations of thought and action: A social cognitive theory*. Englewood Cliffs ,NJ: Prentice-Hall.

Bandura, A. (1997). *Self-efficacy: The exercise of control*. New York: W.H. Freeman & Company.

Baron, R., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*(6), 1173-1182.

Barroso, J., & Sandelowski, M. (2001). In the field with the Beck Depression Inventory. *Qualitative Health Research, 11*(4), 491-504.

Bastardo, Y. M., & Kimberlin, C. L. (2000). Relationship between quality of life, social support

and disease-related factors in HIV-infected persons in Venezuela. *AIDS Care, 12*(5), 673-684.

Bayer, R., & Stryker, J. (1997). Ethical challenges posed by clinical progress in AIDS. *American Journal of Public Health, 87*(10), 1599-1602.

Beck, A., Steer, R. A, Brown, G. K. (1996). *BDI-II Manual*. San Antonio: The Psychological Corporation, Harcourt Brace & Company.

Berg, K. M., Demas, P. A., Howard, A. A., Schoenbaum, E. E., Gourevitch, M. N., & Arnsten, J. H. (2004). Gender differences in factors associated with adherence to antiretroviral therapy. *Journal of General Internal Medicine, 19*(11), 1111-1117.

Berger-Greenstein, J. A., Cuevas, C. A., Brady, S. M., Trezza, G., Richardson, M. A., & Keane, T. M. (2007). Major depression in patients with HIV/AIDS and substance abuse. *AIDS Patient Care and STDs, 21*(12), 942-955.

Bradley, K. A., Bush, K. R., Epler, A. J., Dobie, D. J., Davis, T. M., Sporleder, J. L., et al., (2003). Two brief alcohol-screening tests from the Alcohol Use Disorders Identification Test (AUDIT). *Archives of Internal Medicine, 163*, 821-829.

Bradley, K. A., DeBenedetti, A. F., Volk, R. J., Williams, E.C., Drank, D., Kivlahan, D. R. (2007). AUDIT-C as a brief screen for alcohol use in primary care. *Alcoholism: Clinical and Experimental Research, 31*(7), 1208-1217.

Bradley, K. A., Maynard, C., Kivlahan, D.R., McDonell, & Fihn, S. D., (2001). The relationship between alcohol screening questionnaires and mortality among male veteran outpatients. *Journal of Studies on Alcohol, 62*(6), 826-833.

Bradley, K. A., McDonell, M. B.., Bush, K., Kivlahan, D. R., Fihn, S. D. (1998). The AUDIT

alcohol consumption questions: Reliability, validity, and responsiveness to change in older male primary care patients. *Alcoholism: Clinical and Experimental Research, 22*(8), 1842-1849.

Braithwaite, R. S., Conigliaro, J., Roberts, M. S., Shechter, S., Schaefer, A., McGinnis, K., et al. (2007). Estimating the impact of alcohol consumption on survival for HIV+ individuals. *AIDS Care, 19*(4), 459-466.

Braithwaite, R. S., McGinnis, K. A., Conigliaro, J., Maisto, S. A., Crystal, S., Day, N., et al. (2005). A temporal and dose-response association between alcohol consumption and medication adherence among veterans in care. *Alcoholism: Clinical & Experimental Research, 29*(7), 1190-1197.

Brantley, P. J., Dutton, G. R., & Wood, K. B. (2004). The Beck Depression Inventory-II (BDI-II) and the Beck Depression Inventory-Primary Care (BDI-PC). In M. Maruish (Ed.), *The use of psychological testing for treatment planning and outcomes assessment: Vol. 3. Instruments for Adults* (pp. 313-326). Mahwah , NJ: Lawrence Erlbaum Associates, Inc.

Broyles, L. M., Colbert, A. M., & Erlen, J. A. (2005). Medication practice and feminist thought: A theoretical and ethical response to adherence in HIV/AIDS. *Bioethics, 19*(4), 362-378.

Bryant, K. J. (2006). Expanding research on the role of alcohol consumption and related risks in the prevention and treatment of HIV/AIDS. *Substance Use & Misuse, 41*(10-12), 1465-1507.

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., Bradley, K. A. for the Ambulatory Care Quality Improvement Project (ACQUIP). (1998). The AUDIT Alcohol Consumption Questions (AUDIT-C): An effective brief screening test for problem drinking. *Archives of Internal Medicine, 158,* 1789-1795.

Caetano, R. (2003). Alcohol-related health disparities and treatment-related epidemiological findings among Whites, Blacks, and Hispanics in the United States. *Alcoholism: Clinical and Experimental Research, 27*(8), 1337-1339.

Caetano, R., Clark, C. L., Tam, T. (1998). Alcohol consumption among racial/ethnic minorities: Theory and research. *Alcohol Health & Research World, 22*(4). Retrieved May 31, 2008 from http://pubs.niaaa.nih.gov/publications/arh22-4/233.pdf

Caetano, R., & Hines, A. M. (1995). Alcohol, sexual practices, and risk of AIDS among blacks, Hispanics, and whites. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology, 10*(5), 554-561.

Canagasaby, A., Vinson, D. C. (2005). Screening for hazardous or harmful drinking using one or two quantity-frequency questions. *Alcohol & Alcoholism, 40*(3), 208-213.

Carmines, E. G., Zeller R. A. (1979). *Reliability and validity assessment*. Beverly Hills, CA: Sage Publications.

Carroll, K. M. (1997). Enhancing retention in clinical trials of psychosocial treatments: Practical strategies. In L. S. Onken, J. D. Blaine, J. J. Boren (Eds.). Beyond the therapeutic alliance : Keeping the drug-dependent individual in treatment, *NIDA Research Monograph 165*, NIH Publication number 97-4142, Rockville, MD. Retrieved July 1, 2008 from http://www.nida.nih.gov/pdf/monographs/Monograph165/Monograph165.pdf

Catz, S., Kelly, JA, Bogart, LM, Benotsch, EG, McAuliffe, TL. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology, 19*(2), 124-133.

Catz, S. L., McClure, J., Jones, G., & Brantley, P. (1999). Predictors of outpatient medical appointment attendance among persons with HIV. *AIDS Care, 11*(3), 361-373.

Center for Substance Abuse Treatment, (2000) *Substance Abuse Treatment for Persons with HIV/AIDS.* Treatment Improvement Protocol (TIP) Series, Number 37. (DHHS Pub. No. (SMA) 00-3410). Washington, D.C., U.S. Government Printing Office. Retrieved July 8, 2008 from http://ncadi.samhsa.gov/govpubs/bkd359/

Cha, E., Erlen, J. A., Kim, K. H., Sereika, S. M., & Caruthers, D. (2007). Mediating roles of medication–taking self-efficacy and depressive symptoms on self-reported medication adherence in persons with HIV: A questionnaire survey. *International Journal of Nursing Studies, doi:10.1016/j.ijnurstu.2007.08.003*.

Chander, G., Himelhoch, S., & Moore, R. D. (2006). Substance abuse and psychiatric disorders in HIV-positive patients: Epidemiology and impact on antiretroviral therapy. *Drugs, 66*(6), 769-789.

Chander, G., Lau, B., & Moore, R. D. (2006). Hazardous alcohol use: A risk factor for non-adherence and lack of suppression in HIV infection. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 43*(4), 411-417.

Chesney, M. A., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J., Zwickl, B., et al. (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: The AACTG adherence instruments. *AIDS Care, 12*(3), 255-266.

Chesney, M. A., Morin, M., Sherr. L. (2000). Adherence to HIV combination therapy. *Social Science & Medicine, 50*(11), 1599-1605.

Christensen, A. J. (2004). *Patient adherence to medical treatment regimens: Bridging the gap between behavioral science and biomedicine*. New London, CT: Yale University Press.

Christensen, A. J., & Smith, T. W. (1995). Personality and patient adherence: Correlates of the five-factor model in renal dialysis. *Journal of Behavioral Medicine, 18*(3), 305-313.

Cohen, S., Mermelstein, R, Kamarck, T, Hoberman, H. (1985). Measuring the functional components of social support. In I. G. Sarason & B. R. Sarson (Eds.), *Social support: Theory, research and application* (pp. 73-94). The Hague: Holland: Martinus Nijhoff.

Conigliaro, J., Gordon, A. J., McGinnis, K. A., Rabeneck, L., & Justice, A. C. (2003). How harmful is hazardous alcohol use and abuse in HIV infection: Do health care providers know who is at risk? *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 33*(4), 521-525.

Conigliaro, J., Justice, A. C., Gordon, A. J., & Bryant, K. (2006). Role of alcohol in determining human immunodeficiency virus (HIV)-relevant outcomes: A conceptual model to guide the implementation of evidence-based interventions into practice. *Medical Care, 44*(8 Suppl 2), S1-6.

Conway, B., Prasad, J., Reynolds, R., Farley, J., Jones, M., Jutha, S., et al. (2004). Directly observed therapy for the management of HIV-infected patients in a methadone program. *Clinical Infectious Diseases, 38 Suppl 5*, S402-408.

Cook, R. L., Sereika, S. M., Hunt, S. C., Woodward, W. C., Erlen, J. A., & Conigliaro, J. (2001). Problem drinking and medication adherence among persons with HIV infection. *Journal of General Internal Medicine, 16*(2), 83-88.

Costa, P., McCrae, RR. (1992). *Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI): Professional manual*. Odessa, FL: Psychological Assessment Resources.

Costa, R. R., & McCrae, P. T. (1999). A Five Factor Theory of Personality. In L. A. Pervin & O. P. John (Eds.), *Handbook of personality: Theory and research* (pp. 139-153). New York: Guilford Press.

Cruess, D. G., Minor, S., Antoni, M. H., & Millon, T. (2007). Utility of the Millon Behavioral Medicine Diagnostic (MBMD) to predict adherence to Highly Active Antiretroviral Therapy (HAART) medication regimens among HIV-positive men and women. *Journal of Personality Assessment, 89*(3), 277-290.

Dawson, D. A., Grant, B. F., Stinson, F. S., Zhou, Y. (2005) Effectiveness of the derived alcohol use disorders identification test (AUDIT-C) in screening for alcohol use disorders and risk drinking in the U.S. general population. *Alcoholism: Clinical and Experimental Research, 29*(5), 844-854.

Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. (2008). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Office of AIDS Research Advisory Council, Retrieved May 2, 2008 from http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

Durvasula, R. S., Myers, H. F., Mason, K., & Hinkin, C. (2006). Relationship between alcohol use/abuse, HIV infection and neuropsychological performance in African American men. *Journal of Clinical & Experimental Neuropsychology, 28*(3), 383-404.

Ediger, J. P., Walker, J. R., Graff, L., Lix, L., Clara, I., Rawsthorne, P., et al. (2007). Predictors of medication adherence in inflammatory bowel disease. *American Journal of Gastroenterology, 102*(7), 1417-1426.

Frank, D., DeBenedetti, A. F., Volk, R. J., Williams, E. C., Kivlahan, D. R., Bradley, K. A. (2008). Effectiveness of the AUDIT-C as a screening test for alcohol misuse in three race/ethnic groups. *Journal of General Internal Medicine, 23*(6), 781-787.

Galvan, F. H., Bing, E. G., Fleishman, J. A., London, A. S., Caetano, R., Burnam, M. A., et al.

(2002). The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: Results from the HIV Cost and Services Utilization Study. *Journal of Studies on Alcohol, 63*(2), 179-186.

Galvan, F. H., Burnam, M. A., & Bing, E. G. (2003). Co-occurring psychiatric symptoms and drug dependence or heavy drinking among HIV-positive people. *Journal of Psychoactive Drugs, 35 Suppl 1*, 153-160.

Galvan, F. H., & Caetano, R. (2003). Alcohol use and related problems among ethnic minorities in the United States. *Alcohol Research & Health*. Retrieved June 12, 2008 from http://pubs.niaaa.nih.gov/publications/arh27-1/87-94.htm

Gordon, A. J., Maisto, S. A., McNeil, M., Kraemer, K. L., Conigliaro, R. L., Kelley, M. E. et al. (2001). Three questions can detect hazardous drinkers. *Journal of Family Practice, 50*(4), 313-320.

Gorsuch, R. L. (1983). *Factor analysis*. Hillsdale, NJ: Lawrence Erlbaum.

Halkitis, P. N., Kutnick, A. H., & Slater, S. (2005). The social realities of adherence to protease inhibitor regimens: Substance use, health care and psychological states. *Journal of Health Psychology, 10*(4), 545-558.

Halkitis, P. N., Parsons, J. T., Wolitski, R. J., & Remien, R. H. (2003). Characteristics of HIV antiretroviral treatments, access and adherence in an ethnically diverse sample of men who have sex with men. *AIDS Care, 15*(1), 89-102.

Haubrich, R. H., Little, S. J., Currier, J. S., Forthal, D. N., Kemper, C. A., Beall, G. N., et al. (1999). The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *AIDS, 13*(9), 1099-1107.

Hawthorne, G., Elliott, P. (2005). Imputing missing repeated measures data: How should we proceed? *Australian and New Zealand Journal of Psychiatry, 39*(7), 575-582.

Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., et al. (2004). Medication adherence in HIV-infected adults: Effect of patient age, cognitive status, and substance abuse. *AIDS, 18 Suppl 1*, S19-25.

Hinte, J. (2007). NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, Utah: www.NCSS.com.

Hogg, R., O'Shaughnessy, M. V, Gataric, N., Yip, B., Craib, K., Schechter, M. T., Montaner, J. S. G. (1997). Decline in deaths from AIDS due to new antiretrovirals. *Lancet, 349*(9061), 1294.

Holmes, W. C., Bilker, W. B., Wang, H., Chapman, J., & Gross, R. (2007). HIV/AIDS-specific quality of life and adherence to antiretroviral therapy over time. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 46*(3), 323-327.

Howard, A. A., Arnsten, J. H., Lo, Y., Vlahov, D., Rich, J. D., Schuman, P., et al. (2002). A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS, 16*(16), 2175-2182.

Howard, K. I., Cox, W. M., Saunders, S. M. (1990). Attrition in substance abuse comparative research: The illusion of randomization. In L. S. Onken & J. D. Blaine (Eds.). Psychotherapy and counseling in the treatment of drug abuse. *NIDA Research Monograph 104*, DHHS Publication number (ADM) 90-1722, p. 66-79.

Johnson, M. O., Chesney, M. A., Goldstein, R. B., Remien, R. H., Catz, S., Gore-Felton, C., et

al. (2006). Positive provider interactions, adherence self-efficacy, and adherence to antiretroviral medications among HIV-infected adults: A mediation model. *AIDS Patient Care and STDs, 20*(4), 258-268.

Johnson, M. O., & Neilands, T. B. (2007). Neuroticism, side effects, and health perceptions among HIV-infected individuals on antiretroviral medications. *Journal of Clinical Psychology in Medical Settings, 14*(1), 69-77.

Justice, A. C., Lasky, E., McGinnis, K. A., Skanderson, M., Conigliaro, J., Fultz, S. L., et al. (2006). Medical disease and alcohol use among veterans with human immunodeficiency infection: A comparison of disease measurement strategies. *Medical Care, 44*(8 Suppl 2), S52-60.

Kenny, D. A. (2008, May 20). Mediation. Retrieved June 12, 2008 from http://davidakenny.net/cm/mediate.htm.

Kleeberger, C. A., Phair, J. P., Strathdee, S. A., Detels, R., Kingsley, L., & Jacobson, L. P. (2001). Determinants of heterogeneous adherence to HIV-antiretroviral therapies in the Multicenter AIDS Cohort Study. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 26*(1), 82-92.

Kline, R. (1998). *Principles and practice of structural equation modeling*. New York: Guilford Press.

Laws, M. B., Wilson, I. B., Bowser, D. M., & Kerr, S. E. (2000). Taking antiretroviral therapy for HIV infection: learning from patients' stories. *Journal of General Internal Medicine, 15*(12), 848-858.

Lazo, M., Gange, S. J., Wilson, T. E., Anastos, K., Ostrow, D. G., Witt, M. D., et al. (2007).

Patterns and predictors of changes in adherence tohighly active antiretroviral therapy: Longitudinal study of men and women. *Clinical Infectious Diseases, 45*(15), 1377-1385.

Lefevre, F., O'Leary, B., Moran, M., Mossar, M., Yarnold, P. R., Martin, G. J., et al. (1995). Alcohol consumption among HIV-infected patients. *Journal of General Internal Medicine, 10*(8), 458-460.

Lerner, B., Gulick, R. M., Dubler, N. N. (1998). Rethinking nonadherence: Historical perspectives on triple-drug therapy for HIV disease. *Annals of Internal Medicine, 129*(7), 573-578.

Loehlin, J. C. (2004). *Latent variable models: An introduction to factor, path, and structural equation analysis*. Mahwah, NJ: Lawrence Erlbaum.

Lucas, G. M., Gebo, K. A., Chaisson, R. E., & Moore, R. D. (2002). Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. *AIDS, 16*(5), 767-774.

Lucas, G. M., Mullen, B. A., McCaul, M. E., Weidle, P. J., Hader, S., & Moore, R. D. (2007). Adherence, drug use, and treatment failure in a methadone-clinic-based program of directly administered antiretroviral therapy. *AIDS Patient Care & STDs, 21*(8), 564-574.

Luszczynska, A., Sarkar, Y., & Knoll, N. (2007). Received social support, self-efficacy, and finding benefits in disease as predictors of physical functioning and adherence to antiretroviral therapy. *Patient Education & Counseling, 66*(1), 37-42.

Macalino, G. E., Hogan, J. W., Mitty, J. A., Bazerman, L. B., Delong, A. K., Loewenthal, H., et al. (2007). A randomized clinical trial of community-based directly observed therapy as an adherence intervention for HAART among substance users. *AIDS, 21*(11), 1473-1477.

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A

comparison of methods to test the significance of the mediated effect. *Psychological Methods, 7*, 83-104.

Maisto, S. A., Conigliaro, J., McNeil, J., Kraemer, K., Kelley, M. E. (2000). An empirical investigation of the factor structure of the AUDIT. *Psychological Assessment, 12*(3), 346-353.

Malcolm, S. E., Ng, J. J., Rosen, R. K., Stone, V. E. (2003). An examination of HIV/AIDS patients who have excellent adherence to HAART. *AIDS Care, 15*(2), 251-261.

McCrae, R. R., Costa, P. T., Jr., Martin, T. A., Oryol, V. E., Senin, I. G., O'Cleirigh, C. (2007). Personality correlates of HIV stigmatization in Russia and the United States. *Journal of Research in Personality, 41*(1), 190-196.

Miller, G. (2004). *Learning the language of addiction counseling* (2nd ed). New York: John Wiley & Sons.

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

Muthen, L. K., & Muthen, B. O. (2007). *Mplus User's Guide,* Los Angeles: Muthen & Muthen.

National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2005). Helping Patients Who Drink Too Much: A Clinician's Guide. Retrieved April 12, 2008 from http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm.

Naimi, T. S., Brewer, R. D., Mokdad, A., Denny, C., Serdula, M. K., Marks, J.S., (2003). Binge drinking among U.S. adults. *Journal of the American Medical Association*, *289*(1), 70-75.

National Institutes of Health. (2001). *NIH policy on reporting race and ethnicity data: Subjects in clinical research*. Retrieved July 12, 2008 from

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html

Nicoll, L., Beyea, SC. (1999). Using secondary data analysis for nursing research. *AORN Journal, 69*(2), 428,430,433.

Nieuwkerk, P., Sprangers, MA, Burger, DA, Hoetelmans, RM, Hugen, PW, Danner, SA, et al., (2001). Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Archives of Internal Medicine, 161*(16), 1962-1968.

Nunnally, J., Bernstein, I. (1994). *Psychometric theory* (3rd ed.). New York: McGraw Hill.

Pach, A., 3rd, Cerbone, F. G., & Gerstein, D. R. (2003). A qualitative investigation of antiretroviral therapy among injection drug users. *AIDS & Behavior, 7*(1), 87-100.

Palella, F., Delaney, K. M., Moorman, A. C. , Loveless, M. O. , Fuhrer, .J., Satten, G. A., et al., (1998). Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *New England Journal of Medicine, 338*(13), 853-860.

Palepu, A., Horton, N. J., Tibbetts, N., Meli, S., & Samet, J. H. (2004). Uptake and adherence to highly active antiretroviral therapy among HIV-infected people with alcohol and other substance use problems: The impact of substance abuse treatment. *Addiction, 99*(3), 361-368.

Parsons, J. T., Golub, S. A., Rosof, E., & Holder, C. (2007). Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: A randomized controlled trial. *Journal of Acquired Immune Deficiency Syndromes, 46*(4), 443-450.

Parsons, J. T., Rosof, E., & Mustanski, B. (2007). Patient-related factors predicting HIV

medication adherence among men and women with alcohol problems. *Journal of Health Psychology, 12*(2), 357-370.

Parsons, J. T., Rosof, E., & Mustanski, B. (2008). Medication adherence mediates the relationship between adherence self-efficacy and biological assessments of HIV health among those with alcohol use disorders. *AIDS & Behavior, 12*(1), 95-103.

Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., et al. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine., 133*(1), 21-30.

Penedo, F. J., Gonzalez, J. S., Dahn, J. R., Antoni, M., Malow, R., Costa, P., et al. (2003). Personality, quality of life and HAART adherence among men and women living with HIV/AIDS. *Journal of Psychosomatic Research, 54*(3), 271-278.

Petry, N. M. (1999). Alcohol use in HIV patients: What we don't know may hurt us. *International Journal of STD and AIDS, 10(*9), 561-570.

Plettenberg, A., Albrecht, D., Lorenzen, T., Paech, V., Petersen, H., Fenner, T., et al., (2001). Resistance analyses in HIV infected patients with a history of multiple antiretroviral treatment regimens. *Sexually Transmitted Infections, 77*(6), 449-452.

Pollack, C. (1999). Methodological considerations with secondary data analysis. *Outcomes Management for Nursing Practice, 3*(4), 147-152.

Powell-Cope, G. M., White, J., Henkelman, E. J., & Turner, B. J. (2003). Qualitative and quantitative assessments of HAART adherence of substance-abusing women. *AIDS Care, 15*(2), 239-249.

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects

in simple mediation models. *Behavior Research Methods, Instruments, and Computers, 36*(4), 717-731.

Reinert, D. F., & Allen, J. P. (2007). The Alcohol Use Disorders Identification Test: An update of research findings. *Alcoholism: Clinical & Experimental Research, 31*(2), 185-199.

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

Rogers, M. E., Hansen, N. B., Levy, B. R., Tate, D. C., & Sikkema, K. J. (2005). Optimism and coping with loss in bereaved HIV-Infected men and women. *Journal of Social & Clinical Psychology, 24*(3), 341-360.

Rueda, S., Park-Wyllie, L. Y., Bayoumi, A. M., Tynan, A. M., Antoniou, T. A., Rourke, S. B., et al. (2007). Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. *Cochrane Database of Systematic Reviews*(4).

Ryan, C. M., Huggins, J., & Beatty, R. (1999). Substance use disorders and the risk of HIV infection in gay men. *Journal of Studies on Alcohol, 60*(1), 70-77.

Ryan, P., & Lauver, D. R. (2002). The efficacy of tailored interventions. *Journal of Nursing Scholarship, 34*(4), 331-337.

Sackett, D., Haynes, RB. (1976). *Compliance with Therapeutic Regimens*. Baltimore: Johns Hopkins University Press.

Samet, J., Horton, NJ, Meli, S, Freedberg, KA, Palepu, A. (2004). Alcohol consumption and antiretroviral adherence among HIV-infected persons with alochol problems. *Alcoholism: Clinical and Experimental Research, 28*(4), 572-577.

Samet, J. H., Cheng, D. M., Libman, H., Nunes, D. P., Alperen, J. K., & Saitz, R. (2007). Alcohol consumption and HIV disease progression. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 46*(2), 194-199.

Samet, J. H., Horton, N. J., Meli, S., Dukes, K., Tripps, T., Sullivan, L., et al. (2005). A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems. *Antiviral Therapy, 10*(1), 83-93.

Samet, J. H., Horton, N. J., Meli, S., Freedberg, K. A., & Palepu, A. (2004). Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. *Alcoholism: Clinical & Experimental Research, 28*(4), 572-577.

Samet, J. H., Phillips, S. J., Horton, N. J., Traphagen, E. T., Freedberg, K. A. (2004) Detecting alcohol problems in HIV-infected patients: Use of the CAGE questionnaire. *AIDS Research and Human Retroviruses, 20*(2), 151-155.

Sankar, A., Wunderlich, T., Neufeld, S., & Luborsky, M. (2007). Sero-positive African Americans' beliefs about alcohol and their impact on anti-retroviral adherence. *AIDS & Behavior, 11*(2), 195-203.

Schroeder, J., Latkin, C. A. , Hoover, D. R., Knowlton, A. R., Zenilman, J., Strathdee, S., Celentano, D. D. (2001). Social factors related to antiretroviral therapy use in injection drug users. *AIDS & Behavior, 5*(4), 363-369.

Sereika, S., Dunbar-Jacob, J. (2001). Analysis of electronic event monitored adherence. In L. Burke & I. S. Ockene (Eds.), *Compliance in Health Care and Research* (pp. 139-162). Armonk , NY: Futura Publishing Co, Inc.

Shields, A., Guttmannova, K., Caruso, J. C., (2004). An examination of the factor structure of the

Alcohol Use Disorders Identification test in two high-risk samples. *Substance Use & Misuse, 39*(7), 1161-1182.

Sikkema, K. J., Kalichman, S., Hoffmann, R., Koob, J., Kelly, J., & Heckman, T. (2000). Coping strategies and emotional wellbeing among HIV-infected men and women experiencing AIDS-related bereavement. *AIDS Care, 12*(5), 613-624.

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

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

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

SPSS Inc. (1989-2007). SPSS 15.0 for Windows (version 15.0). Chicago (IL); www.spss.com.

Stall, R., McKusick, L., Wiley, J., Coates, T. J., & Ostrow, D. G. (1986). Alcohol and drug use during sexual activity and compliance with safe sex guidelines for AIDS: The AIDS Behavioral Research Project. *Health Education Quarterly, 13*(4), 359-371.

Steinbauer, J. R., Cantor, S. B., Holzer, C. E., Volk, R. J. (1998). Ethnic and sex bias in primary care screening tests for alcohol use disorders. *Annals of Internal Medicine, 129*(5), 353-362.

Stilley, C. S., Sereika, S., Muldoon, M. F., Ryan, C. M., & Dunbar-Jacob, J. (2004).

Psychological and cognitive function: Predictors of adherence with cholesterol lowering treatment. *Annals of Behavioral Medicine, 27*(2), 117-124.

Stone, V. E. (2001). Strategies for optimizing adherence to highly active antiretroviral therapy: Lessons from research and clinical practice. *Clinical Infectious Diseases*, *33,* 865-872.

Sobel, M. E. (1990). Effect analysis and causation in linear structural equation models. *Psychometrika, 55*(3), 495-515.

Tabachnik, B., Fidell, LS. (2001). *Using multivariate statistics* (4th ed.). Boston: Allyn and Bacon.

Tucker, J. S., Burnam, M. A., Sherbourne, C. D., Kung, F.-Y., & Gifford, A. L. (2003). Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *American Journal of Medicine, 114*(7), 573-580.

Tucker, J. S., Orlando, M., Burnam, M. A., Sherbourne, C. D., Kung, F.-Y., & Gifford, A. L. (2004). Psychosocial mediators of antiretroviral nonadherence in HIV-positive adults with substance use and mental health problems. *Health Psychology, 23*(4), 363-370.

Turner, B. J., Laine, C., Cosler, L. & Hauck, W. W. (2003) Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users. *Journal of General Internal Medicine, 18*, 248–257.

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

Wainberg, M., Friedland, G. (1998). Public health implications of antiretroviral therapy and HIV

drug resistance. *Journal of the American Medical Association, 279*(24), 1977-1983.

Waldrop-Valverde, D., Ownby, R. L., Wilkie, F. L., Mack, A., Kumar, M., & Metsch, L. (2006). Neurocognitive aspects of medication adherence in HIV-positive injecting drug users. *AIDS & Behavior, 10*(3), 287-297.

Weaver, K. E., Llabre, M. M., Duran, R. E., Antoni, M. H., Ironson, G., Penedo, F. J., et al. (2005). A stress and coping model of medication adherence and viral load in HIV-positive men and women on highly active antiretroviral therapy (HAART). *Health Psychology, 24*(4), 385-392.

West, B. T., Welch, K. B., Galecki, A. T., (2006). *Linear mixed models: A practical guide using statistical software*. Boca Raton, FL: Chapman & Hall/CRC.

Willenbring, M. L. (2005). Integrating care for patients with infectious, psychiatric, and substance use disorders: Concepts and approaches. *AIDS 19*(Suppl. 3), S227-S237.

Williams, R., Vinson, D. C., (2001). Validation of a single screening question for problem drinking. *Journal of Family Practice, 50*(4), 307-312.

Wilson, H. S., Hutchinson, S. A., Holzemer, W. L. (2002). Reconciling incompatibilities: A grounded theory of HIV medication adherence and symptom management. *Qualitative Health Research, 12*(10), 1309-1322.